

ANAEMIA PROBLEMS
IN
RHEUMATOID ARTHRITIS

BY

FRIED NILSSON

1948

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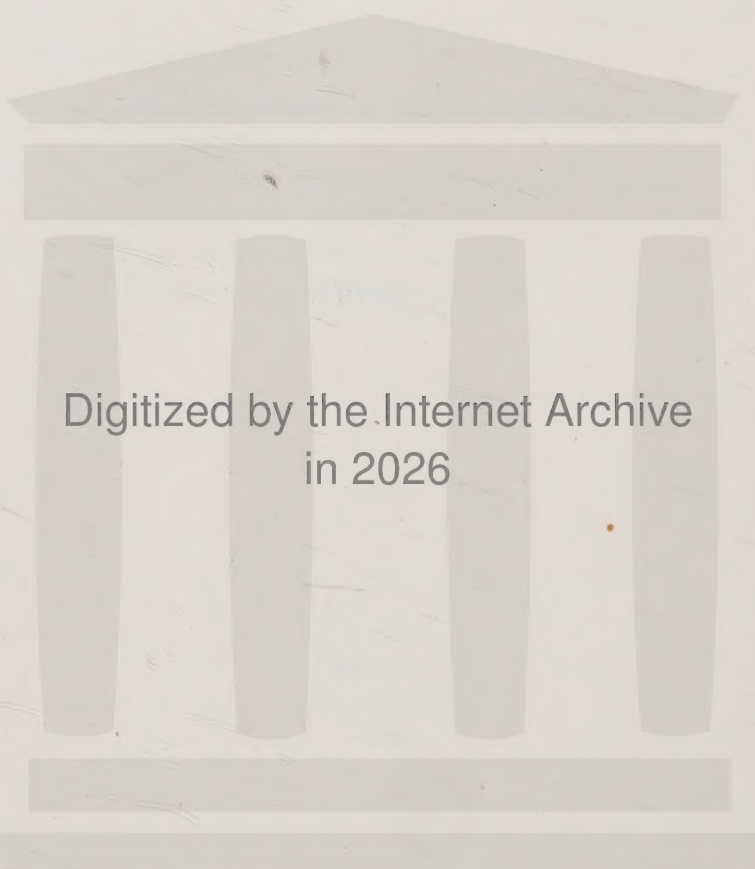
This thesis comes from:

- I. The Medical Department of the Central Hospital, Umeå.
(Chief: Dr S. Ekvall.)
- II. The Medical Clinic of the Academic Hospital, Upsala.
(Then chief: Professor G. Bergmark.)
- III. The State Institute of Human Genetics.
(Chief: Professor G. Dahlberg.)



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Preface.

The theme of this investigation began to interest the author when, as a young physician, he was given the task of studying, by means of Hb determinations, the effect of 1-2 months' iron and arsenic treatment of anaemic cases, most of them chronic polyarthritics. The effect of this treatment proved in most cases to be bad. Current text-books were not enlightening as to why this should be so, and dealt very cursorily with this ordinary type of anaemia, which since that time has become my main object of study. My interest was greatly stimulated by my then Chief, Professor DAVID E. HOLMDAHL, who already then was interested in rheumatic diseases and whom I would like to thank here very warmly.

When later on I began to collect the cases for this study I was particularly indebted to the Senior Physician of the Medical Department of the Central Hospital in Umeå, Dr SVEN EKVALL. Without his active co-operation, the Umeå material could not have been collected.

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Miss INGEBORG ODENSTAM, laboratory nurse, carried out tests on the Umeå material with untiring energy and interest, and Miss DAGMAR MARK, secretary, has helped me with the task of registration; my thanks to both of them.

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Jönköping and Upsala.

April 1948.

Fried Nilsson.

CHAPTER I.

Survey of the literature.

Survey of the literature before 1900.

It is pointed out in particular by Naegeli (1931) and Castle and Minot (1936) that there are few, if any, accurate and detailed observation on the nature of anaemias in the infectious disease states. During recent years, however, interest in this group seems to have increased (see below: Dahl (1942); Saifi and Vaughan (1944); Cartwright, Wintrobe and co-workers and Hemmeler (1946). But it is noteworthy that there are very few direct investigations of recent date on any adequate materials, particularly as this group of anemias is probably the largest of all: it has, however, been referred to on small materials in connection with studies into other forms of anaemia.

Scattered references to anaemias in infectious and infectious-toxic states are also to be found from quite an early date in essays published in very different kinds of periodical. There is apparently no general summary of our knowledge in this field, though Cartwright, Wintrobe and co-w. and Hemmeler gave in 1946 a short survey of certain data from the last few years. The present author has therefore thought it necessary to give a comparatively extensive survey of the investigations which have been made, without, however, claiming that it even approaches completeness. From older works, in particular, it was necessary to mention only the more important studies.

It may be mentioned here that, as regards certain details, the literature of the 19th century provides more points of interest than does that of the 20th.

It is hardly indicated to review the whole early literature. Even the literature after 1900 does not always make comparisons between the different investigations possible. The normal values are often not given, and not only have the measurement errors — especially for haemoglobin — been very great, but the haemoglobin values are given in relative numbers — sometimes even in literature from latter years — without any data which would make possible their conversion into absolute figures.

A work deserving to be mentioned first was published by Andral and Gavarret in 1842. This dealt to a large extent with precisely the state of affairs in the infectious states. Some further studies published during the 50 years immediately following should also be mentioned, since they give facts about this form of anaemia which have not subsequently been sufficiently taken into account, or which seem to have been forgotten.

Andral and Gavarret used the following technique: Blood was tapped into two vessels. The blood in one vessel was whisked up, to determine the amount of fibrin, while that in the other was left to coagulate. The fibrin, the red corpuscles and the quantity of solid ingredients in the serum of the blood was then measured, and the figures obtained given in parts by weight per 1000 parts whole blood. The normal figures for fibrin were 2-4 parts by weight, and for red corpuscles 110-140. With this method they were able to show very great falls in the red corpuscles in acute diseases such as erysipelas, rheumatic fever, acute pleuritis and acute peritonitis: this was even more the case if the sample was taken any time later than immediately after the onset of the disease; these falls showed a plain, though not altogether constant, parallelism with the rise in the fibrin content, measured at the same time. These investigators also noted the pronounced buffy coat in these conditions. In 4 of 10 investigated cases of subacute or chronic rheumatoid arthritis, they were able to

show up to 70-90 parts by weight lowered values for the red corpuscles, while the remaining 6 cases were less affected. Many cases of pulmonary tuberculosis showed a similar state of affairs. Typhus and smallpox did not affect the red corpuscles so much, and measles did not affect them at all. Their values in chlorosis stood at 30 parts by weight, with normal fibrin content in most cases. Popp (1845) and Becquerel and Rodier (cit. Sørensen) made similar observations.

These investigations already indicate the laws followed by the red blood corpuscles and the protein constituents of the blood in the infectious states, and it is only to be regretted that later investigations did not proceed on these lines. Instead, investigators began to count the red blood corpuscles, and subsequently to determine the haemoglobin content of the blood.

Sørensen counted the red corpuscles (1877), and found lowered numbers in pneumonia and rheumatic fever: he pointed out that the latter complaint was characteristic in producing a particularly high degree of anaemia. He also pointed out the occurrence of two types of anaemia — one where the number of red corpuscles was not changed, and the other where it fell.

Another noteworthy study is Laache's large work on anaemic states (1883). He used Malassez's counting method and haemoglobinometer, described in 1877. (For the history of the methods of determination, see Leepin's work of 1891, and Grawitz, 1896). With these he studied the state of the blood in normal material and infected material. The Hb figures were given in mgm Hb/mm⁻³ blood, and were, for 30 normal men, 0.112 (range of variation 0.125-0.098) and for 30 women 0.099 mgm (range of variation 0.109-0.084). For the red blood corpuscles, the mean was 4.97 million/mm³ for men, and 4.43 for women: the difference between the highest and the lowest figure was about 22 %. His values can be taken as fairly representative, even by modern standards. He was able to show anaemia in typhus and syphilis, as also in nephritis and tuberculosis, and to demonstrate that the blood values during convalescence rose.

In his comprehensive work of 1889 Hayem — one of the pillars of the earlier haematology — also handles infectious anaemia. He considers it likely that both an increased decomposition of the blood and a decreased production of new blood are responsible for the anaemia in the infectious diseases. He studied the number of red blood corpuscles, particularly in pneumonia, and found their number to be smallest at the crisis, returning more or less slowly to normal during convalescence. He submitted a copious material in the form of curves to illustrate this, which curves would really repay studying as such. Unlike several of his contemporaries, Hayem was not particularly interested in haemoglobin.

Hayem's chapter on the symptomatic anaemias (anaemia during another disease) has a very wide scope. He deals with the state of affairs in pneumonia, pleuritis, erysipelas, scarlatina, smallpox, measles, rheumatic fever, typhoid fever, malaria, syphilis, tuberculosis, and liver and kidney diseases. He finds rheumatic fever to cause an unusually strong reduction in the red blood corpuscles. Further, when this disease is treated with salicylic acid, the attacks become short and, as a result, the anaemia grows less pronounced. In their often quoted essay, Meersseman, Friess and Lemaitre (1932) have plainly misunderstood this statement of Hayem's, giving it as their view that the salicylic acid is in itself an antianaemic remedy. Hayem makes another very interesting pronouncement: he says it is no rare phenomenon, particularly in young people who may previously have had a tendency to chlorosis, for the number of red blood corpuscles to show successive reducing during convalescence, so that a more or less persistent, chronic anaemic state arises.

These cases, then, would most nearly be ones combining chlorosis (anaemia due to iron deficiency?) and infectious anaemia. There is a great interest in such cases just now (cf. the present author's work of 1939, where the term «combination anaemia» was launched). In Hayem's cases it must surely be assumed that the patient had been chlorotic even before the onset of rheumatic fever, and that the infection increased the chances of the chlorosis progressing; or possibly that the infec-

tion remained and thus maintains the anaemia component due to infection included in the combination 'chlorosis and infectious anaemia'. Anyway, in a condition of this kind iron therapy should, as in Lindberg's cases of anaemia following influenza 1922, be able to banish that proportion of the anaemia corresponding to the chlorosis, whereas the proportion corresponding to the infection may remain, unaffected. We shall have to return to the question of how to decide the type to which the observed anaemia belongs.

Hayem says that the frequency of anaemia in syphilis is difficult to assess, due to the anaemia's usual combination in such cases with chlorosis. It is also interesting to note that Hayem found pronounced anaemia in tuberculosis. Recent writers claim, doubtless wrongly, that tuberculosis has no very perceptible anaemizing effect.

In a fairly large survey, published in 1896, Grawitz went in some detail into the effect of the infectious states on the blood; this survey can be said to summarise the 19th century literature in this field. There is a large bibliography, and many authors are quoted; Grawitz also point out that the anaemias in the graver of these diseases, above all the septic and pyemic ones, presented considerable changes in form among the red blood corpuscles. With this work, the more descriptive and systematic review of these anaemias can be said to be completed.

There is reason in this connection to mention the extensive investigations of Maragliano and Castellini into the different resistance *in vitro* of the red blood corpuscles in normal material and in infectious and other states (1892): When observed under the microscope, the blood corpuscles in the above-mentioned states showed changes in form and a tendency to disintegration far more readily than normal. As far as the present author has been able to discover, these circumstances have not been re-checked, the only exception to this being the investigation of the osmotic resistance to NaCl solution in a few isolated cases, which gave normal results. Hayem also pointed out that, when treated with Hayem's solution A, the red blood corpuscles show a perceptibly reduced resistance in certain pathological states, primarily in infectious diseases such as typhus and smallpox.

mainly in the form of rapidly developing changes of shape. Further, it was only in the blood of diseased persons that he could find the red blood corpuscles in air-dried native preparations to show *état cribriforme*.

Finally, there is of course reason for accepting the correctness of these data with certain reservations. The investigated cases are comparatively few, and the sources of error of the methods are not known; nor are a number of other important factors. Nevertheless, the indicated changes often agree with present-day observations, and they therefore deserve to be taken into account, particularly as they attracted great interest and also gave rise to pronouncements, which have afterwards been forgotten.

Survey of the literature after 1900.

This year, 1900, can be chosen as a dividing-line between older and newer investigations in this field of haematology. We can now begin to speak about more exact studies. The structure of the counting chamber had reached its present form by that time, the methods of determining haemoglobin had become fairly uniform, and the obtained values more or less comparable with one another. It must, however, be stated that after that date, and even today, there are difficulties in comparing values obtained, since the standardisation of the haemoglobinometers is still not perfect, and the values given are too often relative, being submitted in per cent of uncommunicated absolute haemoglobin figures per volume or weight unit of blood. The staining methods were worked out, and also the haematocrite method, and the colour index set up. At the same time, however, there was a disappearance of the interest in the state of the blood in infections and other diseases in the same category, and this survey must be based on data which has crept into studies with other themes as their main subject. This chapter will contain a general survey of the literature. Information as to details will be found in the different chapters on specific subjects.

It gradually became clear that, if an anaemia is to be adequately characterised, it is not enough to call it primary, secondary, or symptomatic. It became desirable to have further details about the haemoglobin, blood corpuscles, etc., in each case. Volume and saturation indices were drawn up, and also thickness index, by the side of the colour index, drawn up earlier on. The colour index represents the ratio of the average red blood corpuscle's Hb content to that of the average red normal corpuscle, the volume index the ratio of the average single red corpuscle's volume to that of the average normal corpuscle, the saturation index the ratio of the average single red corpuscle's Hb content per volume unit to that of the average normal corpuscle, and the thickness index the ratio of the thickness of the single red blood corpuscle to that of the average normal corpuscle. The haemoglobin content of the average red blood corpuscle has also been given in micro-microgrammes, its volume in cubic microns, its haemoglobin concentration per volume unit in per cent and its thickness in μ . and the diameter has been measured in many works.

Capps introduced the volume index into the literature in 1903; he used the haemotocrite method (published in 1890 by S. G. Hedin), which he applied to native blood with a high number of revolutions during a short period. He had a normal material of 10 persons, where the colour and volume index varied 0.9—1.1. He investigated some infected cases, and found a volume index of 0.77 and 0.81 in 1 case of salpingitis and 1 case of tuberculous glands respectively. In 5 cases of acute sepsis and ulcerative endocarditis, the volume index was low, the highest figure being 0.87 and the lowest 0.59. The lower the haemoglobin figure in these latter cases, the lower the volume index and the more pronounced the poikilocytosis, while even in these severe cases the polychromasia was not at all marked. The diameter of the red blood corpuscles showed a slight but perceptible decrease parallel with the volume index. There was a very low diameter, 6.4-6.2 μ , in the cited cases with particularly low volume index. — Summing up, we can say that, in moderate oligocytemia, Capps found the red blood corpuscles somewhat reduced in diameter and

volume; when the oligocytemia was severe, the red blood corpuscles became smaller and probably also thinner than normal and — since the colour index was given as very low — very likely poor in haemoglobin, too. Capps did not determine the saturation index. However, he had another group which he called severe chronic anaemias, a mixed material of different chronic states; in these he found a lowered volume index only in 3 cases, whereas other cases, while showing quite pronounced anisocytosis, had only slightly lowered or even raised figures for their volume index. Very little attention seems to have been given to Capps's work, and in 1931 Osgood, Haskins and Trotman stated that this fact held up the development of haematology as regards precision in anaemia diagnostics for at least 25 years.

Hedin's saturation index was elaborated by Bönninger, as published in his work 1919. The interim had seen publications by Wroth, Larrabee and Alder, but these have not been available for my inspection. Bönninger called this index the *Farbeindex-Volumen*, as against the *Farbeindex-Zahl* (volume index). He pointed out that a microcytosis is present in certain infectious and infectious-toxic states, and as far as the present author can discover, was the first to state that a low colour index need not indicate hypochromia in the single red blood corpuscle, but may be due to microcytosis. He makes a distinction between true and false hypochromia. In the former there is a low colour index and a low saturation index, whereas the latter shows a low colour index and a low volume index, while the saturation index is normal. Judging from the literature no regard has been paid to this observation by Bönninger.

In 1921 Gram determined the volume index but had no infected material. In 1922 Carrie Froehlich expounded methods and index determination, where she accepted Bönninger's indices. She had only 2 certain infectious cases in her material, and of these one case of skeletal tuberculosis showed anaemia with relatively large blood corpuscles and true hypochromia. Csaki found 1922 hypochromia and microcytosis in a small material of 'secondary anaemias'.

Haden's work of 1923 was, as far as the present author has been able to ascertain, the first embodiment of the interest of the American medical world in these indices and absolute figurer. His normal figures will be given in another context. He investigated a few cases of infectious disease states, to be found under the heading 'haemolytic secondary anaemias'; the material is mixed and difficult to assess. All cases showed anaemia. In the majority of cases he found a normal colour index. In some cases there was a lowered volume index, indicating microcytosis, and Haden stated this was because these cases had long been anaemic, or had been for a long time under some harmful influence. In these cases the saturation index was only just below normal.

In their work of 1931, Osgood, Haskins and Trotman also deal with the infectious anaemias. Their normal material will be dealt with later on. Their material covered 23 cases (7 cases of nephritis, 5 cases of sepsis, 2 cases of cholecystitis, 3 cases of chronic sinusitis, 1 case each of pyonephrosis, acute tuberculosis, acute polyarthritis, and pneumonia 9 days after the crisis, and 2 cases of hepatitis); all except the cases of hepatitis and pneumonia had anaemia of varying degrees and a lowered cell-volume figure. The colour and volume indices were lowered beyond the normal limits in a considerable number of cases, and were parallel with one another, indicating the presence of microcytosis and, consequently, of false hypochromia; the normal saturation index in the majority of cases was also in favour of this. Great interest attaches to the circumstance that the saturation index in some cases was unquestionably lowered, and that therefore a true hypochromia was present. Unfortunately, iron therapy was not attempted in these cases. Four cases were reported to have had *haemorrhages*, as well as infections, and in these cases, too, the saturation index was lowered. These cases were not treated with iron, either. They are particularly interesting as being probable exponents of a form of anaemia mentioned earlier on in this survey, namely the so-called combination form — a combination of an iron-sensitive anaemia of iron-deficiency type and an infectious anaemia.

In 1930 and 1934 Wintrobe divided the anaemias according to the size of the blood corpuscles and the haemoglobin content, describing *inter alia* a small material of infection cases, which he relegated to the group of normocytic anaemias or to the group of simple microcytic anaemias. His material will be treated in more detail later on.

There are, of course, also scattered data on anaemias in different infectious or infectious-toxic states, but the materials are as a rule fairly small and incompletely investigated; nor have they received any systematic revision, so that it is only possible to gather from them the already known fact that anaemia occurs in certain cases of such states. — A special chapter will be devoted to the investigations which have been made into the condition of the blood in chronic rheumatoid polyarthritis, since this has a particular interest for us.

The thickness index will not be dealt with in any detail here. It has been the subject of special studies by von Boros, Gram, Wintrobe *et al.*

Rheumatoid arthritis and anaemia.

Except Andral and Gavarret the earlier literature does not touch on the condition of the blood in chronic polyarthritis. Not even the big text-books have any data on this subject. Apparently it was Faber who in 1913 first pointed to the usual occurrence of anaemia and achylia in this disease. He had a material consisting of 65 cases of chronic polyarthritis, and of these, 6 had a haemoglobin figure of less than 65 %. In a material of 72 cases of rheumatic fever, 2 cases had a haemoglobin value of less than 65 %. There is no indication of the method used for determining haemoglobin, or of what the normal haemoglobin figures were in the method used, but it seems as if the normal values stood at 80 % or over. There is no possibility of transferring the values into grammes of Hb per 100 cc, nor is there any indication of the Hb value necessary for a diagnosis of anaemia. The number of cases where the Hb value was between 65 and 80 % is not given, and nor is the sex distribu-

tion. The deficient data can be explained by the fact that Faber was mainly interested in the problem whether, in these cases, existing achylia could have any causal connection with the anaemia. His clinical findings and conclusions in this connection will be touched on later.

In 1915 Faber's pupil Borries took up the problem of chronic polyarthritis and anaemia for renewed examination. He investigated 69 cases of chronic polyarthritis with Sahli's and Haldane's haemoglobinometer. He gave the Hb values in per cent of the normal figure 100, which corresponds to an O_2 -binding capacity of 18.5 volume per cent = 13.8 gm Hb/100 cc blood. Of these 69 cases, 14 showed an Hb value less than 80 %. This figure (80 %) was set as an upper limit for the Hb values, in order, as the author expresses it, 'to keep the material free of the milder anaemias, which do not have much importance, and which most often readily disappear during the stay in hospital'. He had no normal material, and the sex distribution was not given in the total material, but of the anaemic subjects, 2 were men and 12 were women. Of these 14, 8 had an Hb value of 80-65 %, 3 one of 65-50 %, and 3 one of less than 50 %. A red blood corpuscle count was also made in 8 of the most anaemic cases, and the colour index in all of them was found to stand at less than 1. More detailed figures for sex distribution, number of red blood corpuscles and colour index in these latter cases were not given, and in view of the smallness of the material would probably have little relevance.

In 1916 Hans Jensen worked on the problem of anaemia and chronic polyarthritis, and using Tallquist's method found anaemia occurring in his material of chronic polyarthritis. He found an Hb value of under 60 % in 5 cases of 15, and one of under 80 % in 12 cases of 15. He found the Hb value became less if the articular complaint grew worse.

Summing up, it can be said of these investigations that they show the occurrence of lowered Hb values in chronic polyarthritis, and a lowering that is often considerable.

Using a material of 132 cases, Kahlmeter (1921) studied the occurrence of erythrocytopenia in rheumatic complaints. His material consisted of:

- 1) 23 cases of rheumatic fever (anaemia in 65 % of the cases)
- 2) 5 cases of gonorrheal arthritis (anaemia in 80 % of the cases)
- 3) 17 cases of secondary chronic polyarthritis (joint changes remaining after rheumatic fever) (anaemia in 12 % of the cases)
- 4) 33 cases of primary chronic polyarthritis with fever (anaemia in 55 % of the cases)
- 5) 35 cases of primary chronic polyarthritis without fever (anaemia in 6 % of the cases) and
- 6) 19 cases of osteoarthritis (anaemia in 11 % of the cases).

A proportion of less than 4 million red blood corpuscles per mm^3 was accounted anaemia. The sex distribution was not given in this material. No special reason was given for the choice of the above-mentioned figure for anaemia.

It is plain that the percentages given by Kahlmeter have varying values, since they are based on different sized groups, some of which are very small, especially group 2, which contains only 5 cases.

In all cases of rheumatic disease combined with fever, these investigations showed that the tendency to erythrocytopenia was pronounced, while the age of the patient and the duration of the disease had no influence on the degree of the anaemia; this argues that it was the disease in itself and not, as has often been asserted earlier on, the lack of sun, air and movement that was the essential element producing the anaemic state. This observation is of the very greatest importance, as it gives polyarthritis the central position as symptom-producing cause, and to a great extent does away with the idea that it is the disability due to the disease which causes the symptoms.

Pemberton and Peirce (1927) described an investigation of 1100 civil and military cases of rheumatic diseases. They tabulated the nature of the disease for 1041 cases. The material is seen to be non-homogeneous, comprising not only those having trouble with their joints but also cases of all manner of states of pain, specially of the muscular rheumatism type.

though there are also cases of sciatica and neuritis. In this material, the red blood corpuscles were counted in 700 cases, not described in any further detail. Unfortunately the table made from this information is incorrect, as the group of 4.5-5 million has been skipped. Nor can it be calculated, since in spite of the skipping, the total number of cases agrees with the one given. Nevertheless it is plain that the material contained quite a considerable number of oligocythemia cases, in that 32 % of the men had less than 4.5 million red blood corpuscles per mm³, and 34 % of the women less than 4 million.

The same material has yielded 642 cases on whom Hb determinations were made. These cases were not described in detail, either. The percentual distribution by Hb in men and women was as follows.

Hb %	289 ♂		353 ♀	
40—50	1	0.4 %	3	0.8 %
50—60	8	2.6	12	3.5
60—70	14	5.1	47	13.2
70—80	35	12.1	123	34.4
80—90	86	29.6	111	31.6
90—100	104	36.0	56	16.2
100	41	14.2	1	0.3

Method and normal values were not given. With no special motivation, 81 % and over was taken as normal. On this assumption, 20 % of the men and 52 % of the women had anaemia.

Lottrup (1929) described a material of 80 cases, 72 women and 8 men. The blood had been examined in 76 cases. Nevertheless, the material must be denoted non-homogeneous and hard to assess.

11 cases were given as	1) primary chronic progressive poly-
	arthritis
21 » » » »	2) subacute, subchronic or chronic
	rheumatoid polyarthritis
13 » » » »	3) aftermaths of rheumatic fever
20 » » » »	4) osteoarthritis deformans

and the remaining 11 as 5) gonorrheal and uric polyarthritis, or polyarthritis with positive W. R.

It seems likely that group 2 must be taken to be so-called secondary chronic polyarthritis (i.e. secondary to acute polyarthritis), though the nature of group 3 is then not clear. Group 5 has been left out of the discussion.

The haemoglobin figure was determined with Sahli's haemoglobinometer, standardized by means of a cell count. Values of under 95 for men, and under 86 for women, were taken with no further motivation to indicate anaemia. The results of the investigation were given as follows:

					Hb deficit below the limit given above		
					< 10 %	10—19 %	20—29 %
Of 11 cases in group 1)					2	3	1
» 21 » » » 2)					8	0	1
» 13 » » » 3)					3	0	0
» 20 » » » 4)					3	1	0

The sex distribution in these cases was not given. Group 4 could probably be used as control material, i.e. normal material.

Red blood corpuscles were counted in 40 cases, and in no case did the colour index exceed 1. No further information was given concerning the colour index. No megalocytes were demonstrated. Tables made according to the age of the patients and the duration of the disease show that, insofar as the small material allows of any conclusions at all, the age of the patient had nothing to do with the onset of anaemia, and that in group 1 those cases who had been ill for a long time had anaemia, while no effect from the length of the disease can be traced in groups 2 and 3. If anything, the tendency to anaemia was clear in those cases where the disease was of short duration. However, the smallness of the material must be borne in mind.

Collins (1935) described an investigation of the Hb content in 124 cases of rheumatic complaints (62 men and 62 women; no further details given), of which 41.9 % were given as cases of rheumatoid (infective, atrophic) arthritis. The Hb values

were determined with Sahli-Hellige's haemoglobinometer. If anaemia was taken to mean values less than 14 gm Hb/100 cc blood, 58 % of the men and 77.5 % of the women were anaemic. 6.5 % of the men and 16.2 % of the women showed Hb values of less than 12 gm/100 cc blood. A red corpuscle count was also made on 75 women and 25 men. Normal values were not given, but only 24 women and 2 men had values less than 5 million per mm³. The colour index varied between 0.96 and 0.49 in the 100 investigated cases. The reticulocytes were 5-15 ‰. Nucleated red blood corpuscles were not observed, and the osmotic resistance was normal in 6 investigated cases.

In the differentiation of 170 cases (it does not appear whether the above material of 124 cases was included in this material) according to diagnosis and Hb value, it was found, that the group of atrophic arthritis (including ankylosing spondylitis) had a far higher frequency of anaemia than the two groups of osteoarthritis and non-articular rheumatism (including fibrositis, muscular rheumatism and sciatica), that anaemia was much more common in women than in men, and that the more severe degrees of anaemia were only found in the group atrophic arthritis. The results have been tabulated below.

gm Hb	Atrophic arthritis		Osteoarthritis		Non-articular rheumatism	
	M.	F.	M.	F.	M.	F.
16—17	1	—	3	—	1	—
15—16	—	—	2	1	3	3
14—15	8	8	1	4	10	6
13—14	5	19	3	4	6	7
12—13	7	20	3	1	7	9
11—12	2	10	—	—	1	1
10—11	1	9	—	—	—	1
9—10	—	1	—	1	—	—
9	—	1	—	—	—	—
	24	68	12	11	28	27

Collins claims that the age of the patient does not affect the onset or degree of the anaemia. The same applies to diet, except in 2 cases of non-articular rheumatism, which had been on a meatless diet for some time. They had an Hb value of less than 12 gm, and reacted well to iron treatment. Collins also tried out the effect of iron therapy on 12 other cases, with an observation period of up to 21 days. 7 cases did not react at all, and only 2 cases showed distinct improvement. These circumstances will be dealt with in more detail later. It is of interest to note that Collins observed glossy tongue (definite glossitis) in 2 cases, and tender and brittle finger-nails in numerous cases. This question will also be tackled later.

Summing up the information to be gleaned from the above, in many respects, admirable investigations, we find that anaemia (low Hb value and erythrocytopenia) is present in chronic polyarthritis, and that this is due to the harmful action of the disease itself. There are also good reasons for thinking that the duration of the disease and the age of the patient do not really affect the degree of the anaemia.

Various criticisms have been passed on the above investigations, which when summarised show that a lack of normal material, no motivation for the anaemia boundary-line, withholding of the methods used, no absolute Hb values, no information as to sex distribution, and the smallness of the materials and incomplete description of them all go to justify the pronouncement of Castle and Minot on the anaemias occurring when toxins of internal origin are at work, with the sub-group chronic infections: 'There are few, if any, accurate and detailed observations on the nature of this type of anaemia.'

Rheumatoid arthritis, achylia, and anaemia

To my knowledge, Faber was the first to discuss the problem of achylia in chronic polyarthritis. This he did in 1913, saying that as early as 1907 (together with Lange), and again in 1909, he had pointed to the commonness of achylia in this disease. In his material of 65 cases of chronic polyarthritis, published

in 1913, 15 cases had achylia, and 4 of these latter had an Hb value of less than 65 % with a probable normal value of more than 80 %; only 2 of the remaining 50 cases had such low Hb values, and moreover it was not certain whether these 2 really had anaemia (on Faber's own showing, the investigations were not full enough). These circumstances prompted Faber to link up the achylia with the anaemia in these cases of chronic polyarthritis.

Further investigations have been made into this question, whose results are for greater clarity tabulated on next page in Table 1.

Examination of the gastric juices were in all cases made with Ewald's test meal, acidity being the aspect studied. The first column of the table gives the condition of acidity which each individual author denoted achylia. The term 'achylia' has, as is seen, been interpreted very differently.

Borries' normal figure for Hb is, as stated earlier on, 100 %; and since Haldane's standard is used, the absolute figure is 13.8 gm Hb/100 cc blood, and the distribution in the material is shown above. Borries excludes all cases above the age of 50 years from the material, since the achylia frequency in non-polyarthritic material rises after this age. He finds that achylia becomes more usual, the longer the duration of the chronic arthritis. If the material is arranged as in the table, we get 30 % of anaemics among the achylic subjects, and 26 % among the non-achylic. If the material is rendered in another way, we find 7 cases with achylia among 14 anaemic polyarthritics, and 16 cases with achylia among 36 non-anaemic polyarthritics. Working from the anaemia, then, we find that 50 % of the anaemic cases and 44 % of the non-anaemic cases of chronic polyarthritis have achylia. Unlike Faber, Borries does not believe in the connection between polyarthritic anaemia and achylia. The value of his material and conclusions is, of course, very limited, due to his wide view of the term achylia.

Kahlmeter's figures (1921), which also leave out all cases over 50 years old, show that anaemia is commoner in cases of chronic polyarthritis with achylia than in cases of chronic

Table 1. *Anaemia and achylia in rheumatics according to different authors.*

Faber	1913	No. of cases	Free HCl 0	Anaemia < 65 % Hb	Free HCl ÷	Anaemia < 65 % Hb	-
			15	4	50	2	(? incompletely investigated cases)
Borries	1915	No. of cases	Free HCl 0-10	Anaemia 80 % Hb	65 % Hb	Free HCl 10	Anaemia 80 % Hb
			23	7	4	27	65 % Hb
							2
Kahlmeter	1921	No. of cases	T.a. < 20	RBC < 4 m	RBC > 4 m	all cases	
			19	9	10		
		No. of cases	T.a. > 20				
			28	9	19		
		No. of cases	T.a. < 20				
			12	5	7		primary, and secondary chronic polyarthritis with and without fever
		No. of cases	T.a. > 20				
			16	4	12		
Lottrup	1929	No. of cases	Free HCl 0	Anaemia (men < 95 % women < 86 % Hb)	Free HCl +	Anaemia (Men < 95 % women < 86 % Hb)	
			♂ 6	4	27	10	(groups 1-3)
			♀ 4	4	5	2	(group 1 only)

polyarthritis with acidity values higher than the quoted limit for achylia. A nearer inspection, however, shows that the anaemia is only present in those cases, whether rheumatic fever or chronic polyarthritis, where there is fever, while in the other cases the red blood corpuscles stand at over 4 million per mm³, regardless if achylia is present or not; this suggests that achylia does not in itself play very much part in producing the anaemia. Kahlmeter contends that it is more likely that both symptoms have a common cause, the most plausible one being undeniably the infectious-toxic basic disease — a viewpoint to which Israel Holmgren also subscribed in the subsequent discussion.

Lottrup's material 1929, tabulated above, suggests that this investigator was most inclined to agree with Faber's view of achylia as the cause of anaemia. For the division of the material into groups, see the chapter on rheumatoid arthritis and anaemia.

In 1935 Collins investigated the state of the gastric juice in atrophic arthritis. He treated 69 cases (16 men and 53 women) with fractionated test meal (unfortunately no account of the method is given), and found achylia in 3 men and 23 women, achylia being taken to imply the absence of 'free HCl'. Histamine was not given. In 11 cases of osteoarthritis he found no cases of achylia, and in 20 investigated cases of non-articular rheumatism only 1 case. Tabulating the achylic and non-achylic of atrophic arthritis according to Hb value and colour index, it was found that anaemia was also common among those cases whose test meal had a normal HCl content, and that these latter even included cases where the Hb content was lower than among the achylic subjects. The same thing applied to the colour index: it might be low even in cases with normal HCl content in the gastric juices, and the lowest colour index was found in these very cases. Collins claimed to establish that the observed anaemia was a simple hypochrome type, secondary to the basic disease. Collins's material seems to justify the conclusion that, though achylia was far more common in infectious arthritis than in the other investigated cases, anaemia and achylia were not parallel phenomena.

Summing up, we should be warranted in saying that the investigations were performed on very small materials, which in itself renders the results uncertain, and that — with the reservation made above — hypochylia seems to appear more often in the polyarthritis material than in the normal material. The acidity conditions given do not justify the designation of achylia in its present-day sense. The term 'histaminerefractory achylia' has not been touched on.

In 1939, Edström studied the conduct of the HCl secretion on a large material, 432 cases of primary and secondary chronic polyarthritis; in so doing, he took into account the age distribution, since it is known (cit. Edström: Faber, Hartfall, Keefer and Bloomfield, and others) that the frequency of achylia increases with age. He used the fractionated meal; if the samples were Congo-negative in the four first tubes, he injected $\frac{1}{2}$ mgm histamine. He then found a positive correlation between the degree of severity of the polyarthritis in primary chronic cases and the frequency of achylia, but he also found that a histamine-refractory achylia in any case might be reversible, when the polyarthritis became less severe. He found no correlation between anaemia and achylia, and none between the duration of the disease and the achylia.

Using non-infected material, Odin and Lindgren (1932) studied the relation between the acidity values tested on the same person after Ewald-Boas's test meal and a fractionated test meal respectively. The material consisted of 146 persons who, when Ewald-Boas's test meal was used, proved Congo-negative.

These investigations show that, when the total acidity is > 15 , the Congo reaction is always positive with a fractionated test meal without histamine, and that a histamine-refractory achylia does not occur when the total acidity at Ewald-Boas's test meal is > 8 . When the total acidity at such a test meal is < 8 , a good 50 % of the cases are histamine-negative.

We cannot, of course, assume *a priori* that the conditions in Odin and Lindgren's investigations, which were made on a hospital material of gastric complaints, were the same as in

the polyarthritis investigations presented here. Comparative investigations by the present author do, however, show that conditions were at least of a similar nature in both cases.

How the infectious and infectious toxic anaemias arise.

Any work on these anaemias must almost inevitably involve discussing the interesting, important, but extremely complicated question of their origin, and briefly summarising what is known on this subject.

The quantity of red blood corpuscles and haemoglobin at any one juncture is determined by production and destruction, and equilibrium or variations between these factors gives rise to normalcy or the varying pathological conditions respectively.

The immediate problem in the above anaemias was: Are we confronted with increased destruction or lowered production? Whereas earlier investigators assumed the former situation to obtain, and classified these anaemias as haemolytic, the predominant view nowadays is that they should be relegated to the myelodysplastic group — i.e. those due to lowered production. It may be the anaemia arises from a combination of both factors; this is a third possibility.

When production is prevented by some deficiency, such as iron or the liver factor, the case is simple, and the therapy a matter of course. However, a pernicious anaemia may develop iron deficiency in the process of regeneration, and a haemorrhagic anaemia may develop a liver factor deficiency (Vaughan, own observation). No special deficiency has been demonstrable in the infectious or infectious-toxic anaemias, though naturally an anaemia of this kind may sometimes be combined with a known deficit of some factor. It has sometimes been thought that the chronic infectious anaemias are due to aplasia of the bone marrow. As will be shown later, this view can be rejected, and the question of how these anaemias arise simplified thus: Increased haemolysis or lowered

or inhibited function of the bone marrow? Consequently we have to reckon with the following:

- 1) increased haemolysis
- 2) functional disorders in bone marrow or accessory organ.

The first alternative, i.e. increased haemolysis, embodies the old view, and investigators (e.g. Morawitz) advanced the raised urobilin secretion in the urine in its support. The function of the bone marrow was plainly presumed to be normal or enhanced. At the present time, Heilmeyer and co-workers are probably the foremost representatives of the view that increased haemolysis is present in these disease states.

In some cases the urobilin secretion in states of chronic infection has been determined. Eppinger and Charnas, for example, found normal figures in a case of anaemia and lung tuberculosis in 1913. In 1930 M. Weiss described one case with tubercular glands, and 3 cases with lung tuberculosis, who secreted 54-132 mgm urobilinogen per 24 hours. He sets the upper limit for the normal figure at about 80 mgm per 24 hours. In 1933 Paschkis described a patient with ulcerative endocarditis, who secreted 228 mgm urobilinogen per 24 hours — a very raised value. In their work of 1937, Heilmeyer and Plötner communicated a case of chronic polyarthritis, who secreted 77 mgm urobilinogen per 24 hours and had a U.M.I. (see below) of 19.4; in 1938 Watson described a similar case who secreted 60 mgm urobilinogen per 24 hours. Thus, both normal and raised figures have been elicited for this secretion.

Heilmeyer's investigations of 1931, which led to the setting up of the 'Blutmauserungsindex' — also known as the 'Urobilinmauserungsindex' (U.M.I.) — deserve a closer inspection in this context. By comparing the urobilin secretion with the amount of blood, Heilmeyer was able to show that, in an acute haemorrhagic anaemia, there was a reduction in the urobilin secretion, even with regard to the reduced quantity of haemoglobin. When investigating cases of chronic haemorrhagic anaemias — 3 cases of cancer with anaemia and 1 case of

chronic nephritis with slight signs of uraemia — he was able to show increased urobilin secretion in relation to the quantity of haemoglobin present. The blood picture showed anisocytosis and poikilocytosis and a raised reticulocyte count and, in 2 cases of cancer on which an autopsy was performed, red, regenerative bone marrow. The author concluded he was dealing with raised haemolysis, due to a lowered resistance in the abnormal red blood corpuscles. This may seem plausible, but there are other possible reasons why, in such cases, the urobilin secretion is raised, regardless of whether its production is increased or not; for example a) reduced resorptive power in the intestine; b) defective function in the organs absorbing the urobilin coming from the intestine. It must also be remembered that liver injuries can reasonably be expected to be common in infectious states, producing increased secretion of the urobilin, at any case in the urine. Consequently, objections must be raised to Heilmeyer's view, Indeed, generally speaking, it should be warrantable to say that our knowledge of the state of affairs governing the formation, resorption and final secretion of urobilinogen and urobilin is relatively sketchy, due to the complicated mechanism involved, and that the chemical construction of these substances is so labile, and our methods of quantitative determination so comparatively uncertain, that it is difficult to draw more definite conclusions about the destruction and production of blood from the values obtained in investigations. Added to this, there is the statement of Whipple and co-workers that there is no doubt that urobilin and urobilinogen can also be produced from other body substances than haemoglobin, e.g. the iron-containing cytochrome (the Warburg respiratory factor) and also from substances in the food. In the centrum of these substances they have placed the hypothetical pigment complex. Besides this, we know with some certainty that other secretory products can also be referred to the haemoglobin, such as uroerythrin and the so-called urochrome B (i.e. the urochrome which is precipitated with ammonium sulphate), but we know little of the quantitative relations of these substances to one another and to haemoglobin.

H. Lichtenstein and Terwen, Adler and Bressel, M. Weiss, Belonogowa, Sonnenfeld, Watson, and others, have attempted to divide up the anaemias according to their secretion of urobilin and urobilinogen in the urine and faeces. And such a division is, to a certain extent, feasible, since pernicious anaemia and haemolytic anaemia with jaundice are accompanied by intensive secretion of this kind, while in a large number of other forms it is moderate or low.

Vaughan and Saifi made a very interesting observation in 1939. They had a patient with haemolytic jaundice, whose Hb value could be increased by 19 % without special therapy, although the average daily secretion of urobilinogen was 964 mgm (normal figures are about 280 mgm for men, and about 180 mgm for women). Compared with this, the figures they found in infected cases (10 cases in all of infective endocarditis, suppurative pneumonia, and rheumatic carditis) were low, only in one case slightly exceeding the normal. There was also only one case where the U.M.I. was clearly above the normal limit; in 2 cases it was level with it, and in the remaining 7 cases was considerably below. I take this circumstance to indicate that, if the regeneration mechanism of the organism is functioning properly, anaemia need not follow from the low degrees of haemolysis which could be assumed present in the above-mentioned infectious cases. If the mechanism is upset, there are prospects of anaemia. Cf. author's discussion of the term 'blood balance' in Chapter VIII.

Item 2) in the list (p. 22) now follows as a matter of course. The morphology of the bone marrow will be dealt with later. We shall deal here with a number of observations on the intermediate metabolism, which is tending more and more to take a central place in the question of how the infectious anaemias arise. Whipple and co-workers 1936 were able to observe on 2 of their dogs that the production of Hb decreased if the animals were infected. One of them was infected for 5 months with endometritis; when the source of infection was removed, the production of Hb became normal, though not until after a period during which it was very copious; this suggests that the assimilation during the period

of infection is normal, and that consequently a store was laid up. Experimentally induced terpentine abscesses gave lowered Hb production in the animal. A gall fistula was induced on the ureter of the animal, and subsequently a terpentine abscess. During the abscess period, there was some increase in the bilirubin secretion. According to the interpretation given to this finding, this increase cannot be due to raised degeneration of the blood; it must be due to a disturbance in the intermediate metabolism, most likely through not enough use being made of pigment substances in, for example, the formation of haemoglobin.

In 2 cases of infection (no further details given), Vaughan and Saifi 1939 were able, in conformity with the results of Schreuss 1935 and Rimington 1936 (cit.), to demonstrate increased quantities of coproporphyrine I and III in urine and faeces, and therefore considered it likely that there was some disturbance in the Hb metabolism — in which case, it would be specially in the Hb synthesis. On the other hand they could not demonstrate methemalbumin in the blood in cases of infection — a phenomenon which according to Fairley's investigations argues against any very marked intravasal haemolysis. They take the same view as Whipple and co-workers.

In conformity with earlier investigations, Cartwright and co-w. (1946) were able to show an increased quantity of protoporphyrine in the red blood corpuscle in anaemia accompanying an infection; from this they concluded that the Hb metabolism was disturbed. They find it reasonable to locate this disturbance in the Hb synthesis rather than anywhere else, in view of the observations they made in their studies of the iron metabolism.

Using microbiological methods, Thorell (1947) was able to show in pernicious anaemia and haemorrhagic anaemia an abnormal polynucleotide and haemoglobin composition of the cytoplasm during the cell genesis. Unfortunately he has not investigated any cases of anaemia accompanying an infection. Such an investigation should yield a number of interesting findings.

CHAPTER II.

Normal figures for haemoglobin and red blood corpuscles according to the literature.

An investigation of anaemias in chronic and acute polyarthritis is interesting both for a study of the nature of the infectious anaemias and for the symptomatology of the rheumatic diseases. Before reviewing earlier investigations, we shall touch shortly on the state of affairs in the normal blood picture.

As regards the Hb figure, there are a number of investigations where these figures are given in grammes, and can therefore be compared with one another. We include here those where the number of investigated cases are 20 or more, and where the ages are not less than 18 years for men and 17 years for women. See Table 2 and 2 a.

The investigations into the number of red blood corpuscles in normal material have been taken from more recent times, the above principle being applied — i.e. that the investigated cases numbered 20 or more, and the ages were not less than 18 years for men and 17 years for women. For those figures see Table 3 and 3 a.

For Hb and red blood corpuscles in men, we also refer to Nelson & Stoker's work of 1937, giving tables of the results of 43 investigators on normal persons from different parts of the world; there is also Bierring's work of 1940. Unfortunately I have not had access to the compilations of Kennedy (1939), or of Meyers and Eddy (1939).

Table 2. *Normal figures for hemoglobin in men, not below 18 years of age. Not less than 20 cases.*

Author	Num- ber of cases	Age in years	Gm. % hb	Variation
Williamson 1916	36	20—30	15.80	
1916	104	30—60	16.96	
1916	81	> 60	15.81	
Wintrobe	100	19—30	17.00	Cit. Handbook of Hematology
Gram 1920	72		13.8	Lowest figure 12.5, highest figure 15.1
Haden 1923	20	18—30	15.83	14.2—17.17
1923	20	30—50	15.23	13.8—16.9
Osgood 1926	137	19—30	15.76	13.44—19.03 (90 % of the cases 14—18 gm)
Horneffer 1928	40	19—30	16.06	± 0.14 σ 0.87 . $M \pm 3 \sigma = 18.67 - 13.45$
Foster & Johnson 1931	115	18—30	15.63	± 0.057 σ 0.92 . $M \pm 3 \sigma = 18.39 - 12.87$
Price-Jones & co-w. 1931	100	21—48	14.50	± 0.39 $\frac{13.25-15.99}{96-116 \%}$ 100 % = 13.8 gm Hgb
Millet & Balle-Helaers 1932	50	> 60	13.30	Lowest figure $\frac{9.66}{70 \%}$, highest figure $\frac{16.56}{120 \%}$ (colour index in one case 1.46)
Jervell & Waaler 1934	50	20—30	16.20	Lowest figure 13.8, highest figure 18.5
Linneberg & Schartum- Hansen 1935	51	19—30	15.59	Lowest figure 14.0, highest figure 18.4
Price-Jones & co-w. 1935	90	20—42	14.71	σ 0.76, lowest figure 12.49, highest figure 16.99
Heilmeyer & Household 1936	80	22—64 M = 35	15.99	± 0.12 σ 1.1, lowest figure 12.69, highest figure 19.29
Nelson & Stoker 1937	350	18—65	15.03	12.35 — 18.39
Vahlquist 1941	50	20—30	15.68	± 0.12 σ 0.86 $M \pm 3 \sigma = 18.26 - 13.10$

Table 2 a. *Normal figures for hemoglobin in women, not below 17 years of age. Not less than 20 cases.*

Author	Num- ber of cases	Age in years	Gm. % hb	Variation
Williamson 1916	49	17—30	15.11	
1916	93	30—60	15.95	
1916	71	> 60	15.39	
Wintrobe	50	17—30	13.76	Cit. Handbook of Hematology
Gram 1920	56		11.9	Lowest figure 10.8 highest figure 13.4
Osgood & Haskins 1924	100	17—30	13.69	(90 % of the material 12—15.5) lowest figure 10.98 highest figure 15.77
Schmoll 1931	40	19—27	13.70	± 0.13 $\sigma 0.81$ $M \pm 3 \sigma = 16.13$ — 11.27
Price-Jones & co-w. 1931	100	19—32	13.60	12.42—15.18 gm Haldane's standard: 90—110 % 13.8 gm = 100 %
Millet & Balle-Helaers 1932	41	> 60	13.30	Lowest figure $\frac{8}{65} \frac{97}{\%}$ highest figure $\frac{16.14}{117\%}$
Linneberg & Schartum- Hansen 1935	60	19—30	14.06	Lowest figure 12.1 highest figure 17.1
Heilmeyer & Haushold 1936	80	19—57 $M=30$	14.76	± 0.097 lowest figure 12.15 highest figure 17.37
Vahlquist 1941	50	20—30	13.48	± 0.12 $\sigma 0.87$ $M \pm 3 \sigma = 16.09$ —10.87

As the tables show, the literature yields many reports as to the mean values for normal persons. Figures for the variability have not always been given. This is quite understandable. An attempt to give such figures would make the problem of the normal limits very acute. The investigator must decide on and describe those cases he has selected as being, in his opinion, anaemic. This raises a considerable difficulty which is got over by not discussing the variability at all, but only speaking of normal persons. However, the difficulty is not really overcome, since the mean obtained depends on where the lower limit is fixed. It is therefore not surprising that the normal figures of different investigators in tables 2 and 3 differ appreciably from one another.

But there are authors who have given figures for the variation, in which case they probably set a lower limit to their

Table 3. *Normal figures for red blood corpuscles in men, not below 18 years of age. Not less than 20 cases.*

Author	Number of cases	Age in years	Number of Rbc in millions	Variation
Gram 1920	32		5.37	Lowest figure 4.85, highest figure 5.82
Bing 1921	22	> 60	6.10	4.9—9.8
Haden 1923	20	18—20	5.08	4.52—5.57
» 1923	20	30—50	4.87	4.32—5.46
Osgood 1926	137	19—30	5.39	4.4—6.4 (in 90 % of the cases 4.7—6.1)
Epstein 1928	42	18—33	4.93	Cit. Handbook of Hematology
Horneffer 1928	40	19—30	4.97	± 0.05 $\sigma 0.30$ $M \pm 3\sigma = 5.87-4.07$
Wintrobe & Miller 1929	100	19—30	5.85	4.68—7.53
Price-Jones & co-w. 1931	100	21—48	5.43	± 0.03 $\sigma = 0.30$ $M \pm 3\sigma = 6.33-4.53$
Forster & Johnson 1931	115	18—30	5.26	± 0.024 $\sigma 0.369$ $M \pm 3\sigma = 6.37-4.15$
Millet & Balle-Helaers 1932	50	> 60	3.90	2.32—5.3
Jervell & Waaler 1934	50	20—30	5.52	4.83—6.15
Linneberg & Schartum- Hansen 1935	51	19—30	5.27	4.38—5.97
Price-Jones & co-w. 1935	96	20—42	5.50	± 0.0329 $\sigma 0.3228$ $M \pm 3\sigma = 6.47-4.53$
Heilmeyer & Household 1936	52	M = 40	5.06	
Nelson & Stoker 1937	350	18—65	5.11	4.03—6.70
Vahlquist 1941	50	20—30	5.01	± 0.05 $\sigma 0.36$ $M \pm 3\sigma = 6.09-3.93$

material. If we take such a material, which presents more or less skew distribution, calculate the dispersion and then allow for a range of variation of $\pm 3 \sigma$, we find ourselves outside the set limit. In other words, this method is doubtful. If a lower limit has been set, it will quite simply also be the lower limit for the variation. This brings up the problem of the terms 'normal' and 'abnormal' as compared with the terms 'healthy' and 'ill'. As Dahlberg has pointed out, the boundary-line between normal and abnormal does not always coincide with that between healthy and ill. To find whether the normal cases really are healthy, they must be tested for other factors than Hb and red blood corpuscles, and not until then can one

Table 3 a. *Normal figures for red blood corpuscles in women, not below 17 years of age. Not less than 20 cases.*

Author	Number of cases	Age in years	Number of Rbc in millions	Variation
Gram 1920	56		4.78	Lowest figure 4.21 highest figure 5.33
Bing 1921	21	> 60	5.10	4.2—6.4
Osgood & Haskins 1927	100	17—30	4.80	90 % of the cases 4.3—5.3, highest figure 5.55, lowest figure 4.07
Wintrobe & Miller 1929	50	17—30	4.93	Cit. Handbook of Hematology
Price-Jones 1931	100	19—32	5.01	" "
Schmoll 1931	40	19—27	4.56	± 0.05 σ 0.29 $M \pm 3\sigma = 5.43$ —3.69
Millet & Balle-Helaers 1932	41	> 60	3.90	2.84—6.02
Linneberg & Schartum-Hansen 1935	60	19—30	4.49	3.65—5.07
Heilmeyer & Haushold 1936	52	M = 28	4.55	
Vahlquist 1941	50	20—30	4.41	± 0.05 σ 0.32 $M \pm 3\sigma = 5.37 - 3.45$

speak of a 'normal' material. This does not seem always to have been done. For example, it is not likely that Bing's case with 9.8 million red blood corpuscles per mm^3 is clinically healthy, nor yet Millet and Balle-Helaer's case with 2.32 million red blood corpuscles per mm^3 and a colour index of 1.46.

Let us now touch on the state of affairs at different ages. It is justifiable to assume that this may not be the same in young people as in adults. It can also be assumed that very old persons will show differences from the rest. In adults, however — i.e. persons between 20 and 50 years old — there is no reason to suspect that age will cause any differences. Williamson was probably the first to investigate the age changes in respect of the Hb figure. However, he included relatively few young persons, while his material of very old persons is relatively large. Each age group contains 15-20 cases, except the group over 75 years of age, in which there are 30 men and 23 women.

Table 4. *Influence of age and sex on hemoglobin according to Williamson.*

Age	Number of cases		Grams of Hgb per 100 cc of blood	
	M.	F.	M.	F.
6—10	18	15	14.57	13.70
11—15	17	20	14.48	14.87
16—20	16	15	16.81	15.64
21—25	17	21	17.23	15.03
26—30	19	28	16.41	15.53
31—35	16	16	16.94	15.44
36—40	17	15	16.98	15.36
41—45	15	16	16.85	15.64
46—50	22	15	17.07	15.49
51—55	19	16	16.96	16.08
56—60	15	15	16.97	15.76
61—65	15	16	16.46	15.71
66—70	17	15	16.19	15.51
71—75	19	17	15.22	15.46
> 75	30	23	15.04	15.39

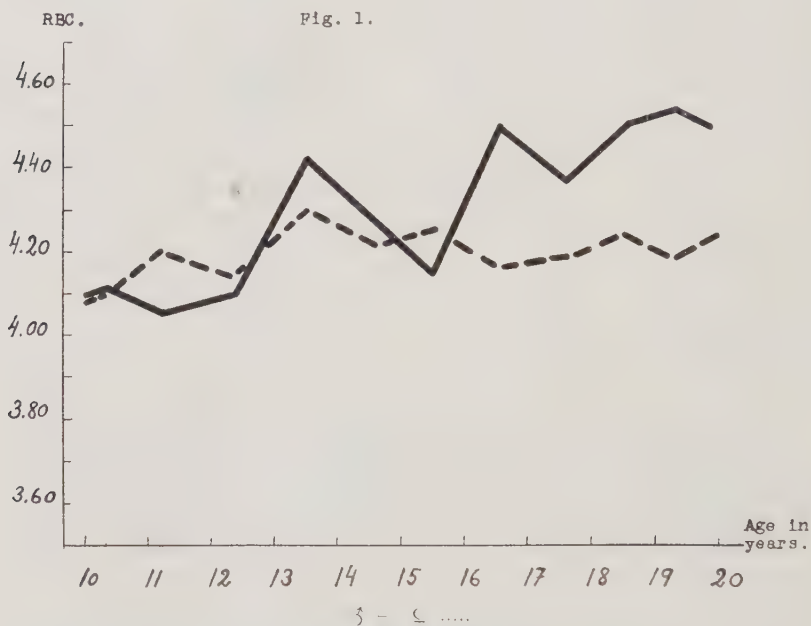
Mainly the same results are reached in the material of 2808 boys and 2916 girls from Norrland, and 236 boys and 267 girls from Skania, on which Odin and Werdinius base their investigations into the age variations in the Hb figure.

A red blood corpuscle count was made on 411 boys and 544 girls in the material, (see Fig. 1 on the following page). As far as it is possible to judge on the basis of their material, it seems that boys and girls have the same number of blood corpuscles at about 10 years of age. The number of red blood corpuscles then increases more for boys than for girls and when they are full-grown, men and women have a difference of half a million.

There were 20-50 investigated cases in each age group. The figures on the axes of the coordination system give the age in years and the red blood corpuscles in millions.

An example of a material definitely including anaemic persons is that on which Odin and Werdinius based their investiga-

tions (1933) into the blood values of adults. This material is, moreover, of particular interest since it was assembled from largely the same part of the country as the present author's. The mean value for their Norrland material (722 men and 962 women) was respectively 90.2 ± 0.38 , σ 10.1; and 80.1 ± 0.37 , σ 11.4. For the Scania material (530 men and 498 women) the mean was respectively 95.4 ± 0.40 , σ 5.1; and 88.2 ± 0.43 , σ 5.7.



The variation coefficient for the Norrland material was 11.2 ± 0.30 for men, and 14.2 ± 0.33 for women. The difference between the variation coefficients is statistically significant, and the anaemia frequency is therefore with every certainty higher in the Norrland material than in the Scanian one — which was what the investigation was intended to show. In any case, it is a familiar fact that women differ from men in the composition of their blood, because they have less red blood corpuscles and a lower Hb content. Tables 2 and 3 also show that the differences as regards blood are by no means small, amounting to about half a million corpuscles and 1 gm Hb.

The range of variation is given in tables 2 and 3. The situation there has been discussed in principle above. It is plain that different authors have different figures for the lower limit of normalcy. This is in all likelihood because they had different materials at their disposal, but it may also be due to their setting different limits for anaemia.

However, unquestionably the best investigation has been made and published by Enghoff in 1937. This investigation stands out by reason of its extraordinary precision. The table 5 outlines his total material (from South, Central, and North Sweden). 20.5 volume per cent O_2 corresponds to 15.3gm Hb per 100 cc blood. It should be mentioned that Enghoff does not find any difference between people living in Norrland and the population in other parts of Sweden which does not agree with what Odin and Werdinius found. It may be possible that Enghoff has sorted out persons with anaemia which the other authors have not done, and that this can explain the discrepancy between their figures. We have, therefore, amalgamated his materials from different parts of Sweden, since there is no noteworthy difference between them. In regard to Enghoff's normal figures, see also Chapter III.

Table 5. *Enghoff. Cases from the whole of Sweden.*

M e n :

Age in years	Number of cases	Vol. % O_2	σ	Number of RBC in millions	σ	Hemato-crite	σ
10—13	32	17.0 ± 0.25	1.42	4.7 ± 0.06	0.33	37.6 ± 0.46	2.61
14—17	41	18.8 ± 0.25	1.61	5.1 ± 0.09	0.57	41.9 ± 0.53	3.42
18—29	76	20.7 ± 0.14	1.23	5.3 ± 0.04	0.38	44.6 ± 0.27	2.31
30—59	40	20.0 ± 0.29	1.82	5.1 ± 0.07	0.42	43.4 ± 0.59	3.70
60—79	15	19.6 ± 0.40	1.55	5.0 ± 0.12	0.45	43.0 ± 1.23	4.76

W o m e n :

10—13	41	17.5 ± 0.15	0.94	4.7 ± 0.05	0.34	38.8 ± 0.26	1.65
14—17	40	17.3 ± 0.14	0.89	4.7 ± 0.05	0.30	38.6 ± 0.34	2.14
18—29	56	17.4 ± 0.23	1.72	4.6 ± 0.03	0.25	38.7 ± 0.29	2.18
30—59	41	18.0 ± 0.24	1.72	4.7 ± 0.06	0.38	39.5 ± 0.57	3.64
60—79	9	19.3 ± 0.32	0.96	5.0 ± 0.08	0.23	42.4 ± 1.15	3.46

The data in the table 6 have been taken from Enghoff's age groups 18-29 years and 30-59 years, which have been lumped together to give as large a material as possible.

Table 6. *Different laboratory figures according to Enghoff.*

		18—59 years			
	Num- ber	M $\pm$ ϵ (M)	σ	M + 3 σ	M—3 σ
		M e n :			
Vol. % O ₂	116	20.46 $\pm$ 0.14	1.50	24.96	15.96
Number of RBC in millions	116	5.23 $\pm$ 0.04	0.41	6.46	4.00
Hematocrite	116	44.19 $\pm$ 0.27	2.92	52.95	35.43
		W o m e n :			
Vol. % O ₂	97	17.65 $\pm$ 0.18	1.75	22.90	12.40
Number of RBC in millions	97	4.64 $\pm$ 0.03	0.32	5.60	3.68
Hematocrite	97	39.04 $\pm$ 0.30	2.92	47.80	30.28

What is meant by anaemia.

When, as appears from what has been said above, there are so many different accounts as to the extent of the normal variation in Hb etc., it is not surprising if one's ideas of where anaemia begins or ends are uncertain. We might just mention that there are no data as to this in current text-books. The question is more or less skirted round. We shall be returning to this matter later.

It is obvious that very low values imply anaemia, but one is very doubtful where to draw the line between what is and is not anaemia. To a certain extent, this is strange, since iron therapy on the grounds of anaemia is a usual thing for practising physicians to apply. When a patient complains of tiredness and feels out of condition, such therapy is often resorted to when no other failing can be seen. It seems that in this

situation the need would be felt of a clear definition of the term 'anaemia'. Actually, the fact probably is that there is a certain boundary region where some people contract symptoms and others do not. In other words, certain persons can stand a lower Hb value than others without feeling ill. Actually, only a few authors have set a definite boundary for anaemia. Heilmeyer, for example, puts it at less than 90 % Hb and fewer than 4.5 million red blood corpuscles for men, and less than 80 % Hb and fewer than 4.0 million red corpuscles for women. He puts the normal figure for men at 100 % Hb = 16 gm % Hb; his motivation is that blood containing 5 million red blood corpuscles per mm^3 has a Hb content of 16 gm/100 cc blood. The normal blood value for women is at 90 % Hb, corresponding to 14.5 gm % Hb. The normal range of variation for Hb in men is set at 90-110 % (14.5-17.6 gm%), and for women at 80-100 % (12.8-16 gm%). But even Heilmeyer does not motivate the limits set for anaemia with clinical observations, or in any other way.

Linneberg and Schartum-Hansen also set a limit for anaemia < 99 % Hb for men, and 90 % Hb for women: corresponding red blood corpuscle figures are 4.7 million and 3.6 million. 100 % Hb is then equal to 13.8 gm Hb 100 cc blood. No further explanation is given for their choice, but they say that values below the limit given 'are probably as a rule pathological'.

Kolmer and Boerner's text-book of 1945 gives the normal Hb figure as 14-17 gm/100 cc blood for men, and 12-16 gm/100 cc blood for women. Corresponding figures for red blood corpuscles are 4.5-6 million/ mm^3 and 4.2-5.4 million/ mm^3 . They do not say on what these figures are based. Presumably they mean that persons with values below those figures for Hb and RBC are anaemic.

The way in which the problem of the term 'anaemia' is solved is typified by the expression commonly used in definition: 'If the boundary-line for anaemia is set at the value x, then so and so many cases will be anaemic.'

Concerning indices and absolute figures for the relation between haemoglobin and red blood corpuscles.

1) Normal persons.

As well as data for the normal figures for Hb and red corpuscles and their variation, there are also figures for indices and their variations, and also absolute figures for the relation between Hb and red blood corpuscles, and the variations of these figures. The indices concern colour, volume and saturation, and the absolute figures are for mean corpuscular haemoglobin (expressed in micromicrogram, $\gamma\gamma$) and abbreviated M.C.H., mean corpuscular volume (expressed in cubic microns, μ^3), abbreviated to M.C.V., and mean corpuscular haemoglobin concentration (expressed in %), and abbreviated M.C.H.C.

The colour index gives the ratio of the average red corpuscle's Hb content to that of the average normal red blood corpuscle, the volume index the ratio of the average red corpuscle's volume to that of the average normal red corpuscle, and the saturation index the ratio of the average red corpuscle's Hb content per volume unit to that of the average normal red corpuscle.

The usual formula for calculating the *colour index* is:

Per cent of normal haemoglobin concentration

per cent of normal erythrocyte count

for the *volume index*:

mean corpuscular volume — patient

mean corpuscular volume — normal

for the *saturation index*:

mean corpuscular haemoglobin concentration — patient

mean corpuscular haemoglobin concentration — normal

The formula for calculating *M.C.H.* is:

haemoglobin in grams per 100 cc of blood $\times 10$
erythrocytes in millions per cubic millimeter

for *M.C.V.*:

<u>volume of packed cells per 100 cc of blood</u>	
<u>erythrocytes in millions per cubic millimeter</u>	10
and for <i>M.C.H.C.</i> :	
<u>haemoglobin in grams per 100 cc of blood</u>	
<u>volume of packed cells per 100 cc of blood</u>	100

As appears from the above, normal values are needed for calculating indices, and for a comparison between the indices of different authors it is necessary to know not only their method errors but also the normal values they used, and the way in which the index was calculated. What makes comparisons of this kind even more difficult is that these indices were not always calculated in the same way, investigators having had different ideas as to the right one.

As far as can be seen, the absolute figures given in the literature at our disposal were calculated according to the above formulas. And in their text-book of 1945, Kolmer and Boerner state that these formulas have the same clinical value as indices and that the practice of using the absolute figures should be adopted — a view with which we agree.

For normal material, the mean for colour, volume, and saturation index is usually given as 1.0, and the limits for the normal as 0.9-1.1. This undoubtedly narrows the normal material both upwards and downwards. Osgood and Haskins give the limits for their normal material as 0.8-1.2 for all indices, which figures can be considered representative.

Enghoff 1937 gives three limits on his carefully studied normal material:

	I	II	III
Colour index	0.79—1.21	0.86—1.14	0.88—1.12
Volume index	0.81—1.19	0.88—1.12	0.90—1.10
Saturation index	0.86—1.14	0.91—1.09	0.92—1.08

In the first alternative there is a probability of 0.3 % that a case in normal circumstances should fall outside the limits given; the corresponding figures for the second and third alternative are 5 % and 10 %.

In the literature the author has found the following normal values for *M.C.H.*, *M.C.V.*, *M.C.H.C.*:

Table 7. Normal figures for the ratio between hemoglobin and red blood corpuscles.

Year	Author	Number	Age in years	M.C.V.	M.C.H.	M.C.H.C.
Men :						
1923	Haden, R. L.	20	18—30	92 (87—95)	31.1 (29.5—33.4)	33.9 (32.2—36.2)
		20	30—50	92 (87—98)	31.3 (29.2—35.6)	33.9 (31.9—35.6)
1926	Osgood	94	19—30	86.1 (71.3—95.5)		
1927	Osgood & Haskins	94	18—30	86	29	33
1929	{ Wintrobe & Miller Wintrobe	109	18—30	85 (63—98) (80 % of the cases 70—87)	29	34
1934	Wintrobe, M. M.	86		86.5 (76—97) σ 3.5	^d 29.1 (24.9—33.3) σ 1.4	34 (29.8—38.2) σ 1.4
1935	Linneberg & Schar- tum-Hansen	51	19—30	84.93 (76.4—94)	29.63 (26.6—34.3)	
1935	Price-Jones & co-w.	99	20—42	85.92 (75.7—96.1) $\pm$ 0.34 σ 3.4	26.86 (23.96—29.76) $\pm$ 0.098 σ 0.979	31.26 (28.17—34.35) $\pm$ 0.103 σ 1.03
1936	Heilmeyer & Haus- hold	52	M = 40		31.7 $\pm$ 0.24 (26.57— 36.83) σ 1.71	
Women :						
1923	Haden, R. L.	12	20—40	92 (91—97)	31.3 (30—33.8)	33.9 (32.2—34.9)
	Osgood	100		88.5		
	Haden	9		92.8		
	Gram & Norgaard	6		$\left\{ \begin{array}{l} 76.5—98.1 \\ M=88.2 \\ \text{cit. Hal. Dow-} \\ \text{ney 1938} \end{array} \right.$		
	Bie & Møller	10		88		
				81.7		
1927	Osgood & Haskins	100	18—30	88	29	32
1929	Wintrobe, M. M. Wintrobe & Miller	61	18—30	85	28	33
1934	Wintrobe, M. M.	101		88 (77.9—99.2) σ 3.4	29.2 (25.1—33.1) σ 1.3	33.5 (29.6—37.4) σ 1.3
1935	Linneberg & Schar- tum-Hansen	60	19—30	86.57 (71.9—98)	31.32 (26.1—38.8)	
1936	Heilmeyer & Haus- hold	52	M = 28		32.3 $\pm$ 0.24 (27—37.6) σ 1.76	

2) Infectious and infectious-toxic states.

Even in their time, Capps and Bönninger found a lowered volume index in certain cases of the above states. In 1923 Haden submitted the following means for 'the secondary haemolytic anaemias', to which category he relegated said disease states: M.C.V.: 86, M.C.H.: 25.2, and M.C.H.C.: 29.5, whereas the normal values were 92, 31.2, and 33.9 respectively. As the variation table shows, these values fall below the lower variation limit for the normal material. The values for pernicious anaemia were 128, 37.5 and 30.2 respectively. As already mentioned, Osgood and Haskins (1932) gave a range of variation in the index of normal material of 0.8-1.2, whereas in infectious states the colour index varied between 0.6-1.2, the volume index between 0.6-1.2, and the saturation index between 0.8 and 1.2.

In his works of 1930 and 1934, Wintrobe classified the anaemias according to the values he found for the submitted absolute figures, the different groups yielding these results:

1) for the normal red blood corpuscle

volume M.C.V.	Hb content M. C. H.	Hb concentration M. C. H. C.	diameter
in micrones ³ (μ^3)	in $\gamma\gamma$	in %	in μ
80—94	27—32	33—38	6.7—8

2) for macrocytic anaemia

95—160	30—52	31—38	7.5—9.6
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3) for simple microcytic anaemia

72—79	22—26	31—38	6.5—8
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4) for hypochrome microcytic anaemia

50—71	14—21	21—29	5.8—7.5
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Generally speaking, group 1) corresponds to the normal state, group 2) to pernicious anaemia, 1) and 3) infectious anaemia and other states, and 4) to anaemia due to iron deficiency.

Wintrobe gives 18 cases of different inflammatory states in his material; for these the means were:

M.C.V.	M.C.H.	M.C.H.C.
87	29	34

These cases he classified among the normocytic anaemias. A similar state of affairs was found in 9 cases of nephritis, and also in cases of aplastic anaemia. 6 cases of pulmonary complaints and 6 cases of infectious arthritis could, however, be relegated to the simple microcytic anaemia group, the values here being respectively

M.C.V.	M.C.H.	M.C.H.C.
76	24	32
75	23	31

No cases among the infectious disease states could be referred to the hypochromic microcytic group. M.C.H.C. was only just below normal, and it may be questioned whether any true hypochromia was present — probably not, which is plainly what Winrobe thought, also.

Thus, it can be seen that this method makes possible a more detailed determination of the character of the anaemia. The table lacks one group, normocytic hypochromic anaemias, which might reasonably be looked for at times, for example among the less protracted haemorrhagic anaemias. Saifi and Vaughan (1944) described 7 men, cases of septic conditions, and classified 5 as normocytic and 2 as microcytic anemias (M.C.V. for all was 70.7-84 and colour index 0.53-0.95); they described also 10 female cases of septic conditions, and classified 6 as normocytic and 4 as microcytic anemias (M.C.V. for all was 64-98 and colour index 0.56-0.94). In 1946 Cartwright and co-w. described 16 cases of different infectious conditions in the ages 16-76 years, all male subjects. The value of their demonstration is undeniably restricted by the fact that all except 3 cases had received one or more blood transfusion.

Normal values:

RBC	Hb	Hematocrite	M.C.V.	M.C.H.	M.C.H.C
5.4 ± 0.8	16 ± 2	47 ± 5	87 ± 5	29 ± 2	34 ± 2

values of 16 cases of given infectious states:

3.43—4.57	8.3—12.3	28.7—40	67—89	17—30	28—34
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It is quite clear that microcytosis was present in certain cases. It is also likely that there were a few isolated cases of true hypochromia, to judge from the lowest values for M.C.H.C. (corresponding to the saturation index).

CHAPTER III.

Methods.

Methods used in the Umeå material.

The same methods of determination were used throughout the material. The same apparatus was used the whole time, the reagents were prepared by the same person and, apart from short periods of time, the values were read off by the same person.

The Hb value was in all cases recorded by an Autenrieth-Königsberger haemoglobinometer. Blood was taken from the finger-tip, care being taken to see that the flow was abundant. When taking samples, mixing-tubes were used, into which were pipetted 1980 mm³ N/10 HCl, and after that 20 mm³ blood. In such material no systematic difference is then demonstrable between venous blood and 'capillary blood' (Enghoff 1937). The reading off was done after about 30 minutes on a standardised haemoglobinometer with a constant source of light. The apparatus was standardised in 1940 and 1942 at the Physiological Institution of the University of Upsala by laborator Enghoff. No material change in the light absorption of the colour wedge could be shown at the later check. The standardisation was so made that 15.3 gm Hb per 100 cc blood corresponded to 100 % Hb. The values were noted in % Hb. A conversion table is given below, to make possible a rapid conversion of the Hb values into absolute figures in grammes. The red blood corpuscles were counted in Bürker's counting chamber, each time taking 16 C + D squares. Dilution 1 : 200. The samples were taken simultaneously with the Hb in an Ellermann tube, into which 10 mm³ blood had been placed in 1990 mm³ Hayem's solution. The dilution was then mixed in an electric corpuscle mixer.

Table of comparison between gm Hb per 100 cc blood and % Hb.

%	gm	%	gm	%	gm
120	= 18.4	95	= 14.5	70	= 10.7
115	= 17.6	90	= 13.8	65	= 9.9
110	= 16.8	85	= 13.0	60	= 9.2
105	= 16.1	80	= 12.2	55	= 8.4
100	= 15.3	75	= 11.5	50	= 7.7

Conversion to Haldane's scale is made by multiplying the percent figure by 1.11.

The colour index was calculated according to the formula $\frac{\% \text{ Hb}}{\text{RBC} \times 20}$. If gramme values are used for the Hb, 3.06 is substituted for 20 in the lower part of the fraction.

The *reticulocytes* were stained with brilliant cresyl blue, dissolved in physiological NaCl solution, after which fixation was made in methyl alcohol and contrast staining by Giemsa's method. The figures give the number of reticulocytes per 1000 examined cells.

Fahraeus's sedimentation reaction is an important part of the investigations. Westergren's method with 3.8 % sodium citrate solution was used, and the values given in mm per hour.

The *serum bilirubin* was determined with Hijmanns van den Bergh's original method, direct and indirect method. The figures give the values for the indirect method expressed in 1 : 200,000 according to current custom.

In the *indirect method*, 2 cc of 96 % alcohol was added to 1 cc serum. The mixture was shaken and centrifuged. To 1 cc of the alcohol centrifugate was added $\frac{1}{2}$ cc 96 % alcohol and $\frac{1}{4}$ cc of the mixture of the diazo reagents. Results were read off after 5 minutes with Autenrieth-Königsberger's apparatus, with a freshly prepared standard. The standard was prepared thus: Take 3 cc of standard initial solution II, 3 cc of the 10 % ammonium rhodanide and 12 cc of ether. The stained ether extract is poured into the standard wedge. The standard initial solution II is prepared from 20 cc standard initial solution I + 50 cc 25 % HCl + 430 cc distilled water. Standard initial solution I consists of 0.1508 gm ferri ammonium sulphate, dissolved in 50 cc HCl (sp. w. 1.19), after which it is diluted to 100 cc.

The *direct method* is made with $\frac{1}{2}$ cc serum + 1 cc distilled water + 0.38 cc of the mixture of the diazo reagents (0.3 cc diazo reagents I + 10 cc diazo reagent II). Diazo reagent I consists of

0.5 sodium nitrate dissolved in 99.5 cc distilled water, and diazo reagent II of 1 gm sulfanilic acid + 15 gm 25 % HCl, diluted with distilled water to 1000 gm.

The measurement of the diameter of the red corpuscles was in this material done with the 'wet method'. A Pasteur pipette was filled with blood, which was allowed to coagulate. After retraction of the coagula, the pipette was broken in two and the diameter of the corpuscles measured in their serum with an immersion lens and measuring ocular. The magnification was determined in an object micrometer.

100 cells were measured in each sample. If the red blood corpuscle was oval, the mean of both diameters was taken. The measurements were made in half and whole gradations on the scale of the micrometer. Thus, each whole grade on the scale corresponds to 1.66 μ . The average was in every case given as the mean diameter. The following boundary values for the measurements were used, and the number of red blood corpuscles has in each group been given as a percentage: 5, 5.83, 6.67, 7.5, 8.33 and 9.16 μ .

The urobilin and urobilinogen in the urine were determined by passed samples of morning urine. It was of course necessary to take such samples for the urobilinogen. In normal material tested with Ehrlich's reagent, the urobilinogen value was small, or usually negative, and the same was true of the amount passed in 24 hours.

The urobilin in the urine was determined quantitatively as follows. 5 cc urine and 5 cc saturated zinc acetate solution were mixed and 2 drops of diluted iodine spirit was added, shaken, left to stand for 1 hour, and then filtered. 2 cc of this filtrate were pipetted into tubes each containing 2 cc filtered saturated zinc acetate solution diluted with an equal quantity of distilled water. 2 cc of the contents of the tube first in order were then introduced into the next tube, and so on, the solutions given between which fluorescence ceases.

The serum iron was determined by the methods given by Heilmeyer and Plötner (1937).

Remarks on the method used:

The blood was taken, if possible without stasis, with platinum iridium needles. It cannot be stressed too strongly how much the efficacy of this method depends on cleanliness in handling, premises, reagents and glass vessels used. Each vessel was left over night in bichromate sulphuric acid, rinsed with hot water from the tap, and then with redistilled water. We made the reagent solutions ourselves. The trichloro-acetic acid was, when necessarily, redistilled in glass.

The statement in the original description of the method calling for the use of Schleicher & Schüll's filter No. 589 proved to be misleading, since only filter No. 589³ is free from iron. Other filters belonging to this number contain iron to a greater or lesser extent, sometimes so much so that certain filters may be tinged brown by it. The iron can be washed out, but in No. 589³ this is not necessary.

The final volume was not measured by us in a pipette, but was calculated, since only the NH_3 and H_2SO_4 quantities vary from analysis to analysis.

Test meal: I. Ewald-Boas's test meal. 1) determination of retention. Red whortleberries given for supper, and the tube is introduced in the morning before the subject has eaten. 2) test breakfast, consisting of 35 gm white bread and 300 gm weak tea without milk or sugar. Withdrawal after 30 minutes from the beginning of the meal. Titration of free HCl with N/10 NaOH with dimethyl-amidoazobenzene as indicator, and of the total acidity phenolphthalein as indicator. II. Fractionated test meal: with methylene-blue coloured coffein solution, and possibly, when no free HCl with Congo paper, injection of $\frac{1}{2}$ mgm histamine. Withdrawal every 10th minute: titration in the ordinary manner of free HCl and total acidity.

Methods for the Upsala material.

The Upsala material was investigated in the same manner, in essentials, but greater precision was aimed at. Venous blood was placed in heparinised tubes. The Hb was read off in Autenrieth-Königsberger's apparatus, standardised at $15.3/100 \text{ cc blood} = 100 \%$. Each Hb figure is the mean of 5 readings. The red blood corpuscles were counted in the same Bürker's counting chamber throughout, and $32 \text{ C} + \text{D}$ squares were counted. The pipettes were checked by weighing.

The haematocrite value was determined according to Dahland in capillary tubes, 50 mm long and with an inner diameter of 0.5 mm, in a specially constructed, covered centrifuge inset for 8 tubes. The centrifugal rate was determined with 'Strobo-Meca', and found to be 6500 revolutions per minute. Centrifuging time was 10 minutes; by this time Koeppe's phenomenon had appeared, and the volume was not changed by further centrifugation. The values are the means of double tests, and although a magnifyingglass was not used in recording the results, the difference between each pair was not often more than 1 %.

The colour index was calculated on the accepted formula $\frac{\text{Hb in \%}}{\text{RBC} \times 20}$ and M.C.V., M.C.H., and M.C.H.C. in the usual manner.

(As for the abbreviation see chapter II.) In part of the material the jaundice index was determined according to Meulengracht. The serum iron was determined as in the Umeå material. For the methods in determining serum copper, see the chapter on serum copper.

Statistical methods.

In the treatment of the material current statistical methods were employed.

The standard deviation (σ) was calculated according to the

$$\sigma = \pm \sqrt{\frac{\sum a^2}{N-1}}$$

formula where a designates the deviation of the individual observations from the mean, and N the number of observations. In the cases where N exceeds 50, the standard deviation was calculated according to the formula

$$\sigma = \pm \sqrt{\frac{\sum a^2}{N}}$$

The standard error of the mean, $\varepsilon(M)$, was calculated according to the formula

$$\varepsilon(M) = \pm \frac{\sigma}{\sqrt{N}}$$

The standard error of percentage values, $\varepsilon(P)$, was calculated according to the formula

$$\varepsilon(P) = \pm \sqrt{\frac{P(100-P)}{N}}$$

where N denotes the number of individuals in the observed material and P the percentage value.

The standard error of the difference, $\varepsilon(D)$, was calculated according to the formula

$$\varepsilon(D) = \pm \sqrt{\varepsilon_1^2 + \varepsilon_2^2}$$

where ε_1 and ε_2 designate the standard errors of the value between which the subtraction is made.

The correlation coefficient was calculated according to the formula

$$r = \frac{1}{N} \sum \frac{a_x}{\sigma_x} \cdot \frac{a_y}{\sigma_y},$$

where a_x and a_y denote the distance of the x and y values from the arithmetical means of the series in question, and σ_x and σ_y the standard deviations of the series; N is the number of observations.

The standard error of the correlation coefficient was calculated according to the formula

$$\varepsilon(r) = \pm \frac{1 - r^2}{\sqrt{N}}$$

Investigation methods. Approximate accuracy.

The method errors were usually determined by investigating 20 samples from the same person, and then getting the standard deviation, σ , from the total. σ is given below.

Double determinations were made for serum iron and serum copper; the difference between the double tests was seldom more than 10 γ % for the iron, and was usually less than 5 γ %; for the copper, the difference was seldom more than 7 γ %, and was usually less than 4 γ %. Double tests were also made for the haematocrite values, the difference between them not often exceeding 1 %.

	Umeå material standard error of the measurement	Uppsala material
Haemoglobin	± 1.10	± 1.08 %
Red blood corpuscles	± 0.066	± 0.072 million
Diameter of RBC	± 0.05	μ
H. v. d. Bergh		± 0.012 mgm %

These errors do not exceed those recorded in the literature.

CHAPTER IV.

Cases investigated.

Normal material.

The present author has assembled two normal materials, one from Umeå and the other from Upsala, which in certain respects differ quite appreciably.

The Umeå normal material consists of hospital patients, most of them suffering from sciatica (disc hernia), with an observation period of about 60 days; the women include more-over cases with a short period of observation, mainly psychoneurotics. The requirements set were that the cases had not shown symptoms of infection nor had had haemorrhages or signs of any other disease that might affect the blood values.

This material is presented in the tables 8, 9 and 10 as regards age distribution, laboratory figures and sex differences. The Upsala normal material will be treated in detail in Chap. XII.

Table 8. *Age distribution of the normal cases from Umeå.*

Age in years	Men	Women
19—24	8	11
25—29	18	9
30—34	13	5
35—39	14	6
40—44	7	10
45—49	4	5
50—54	2	6
55—59	1	11
60—75	—	3
Total	67 ¹	66

¹ Also 1 case without information in regard to age.

Table 9. *Different laboratory figures in the normal cases from Umeå.*
 $M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	M e n			W o m e n		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
Hemoglobin %	68	91.35 ± 0.76	6.29	66	82.91 ± 0.66	5.39
Red blood corpuscles	68	4.844 ± 0.038	0.313	66	4.424 ± 0.039	0.314
Sedimentation rate	67	4.36 ± 0.40	3.28	64	6.63 ± 0.39	3.15
Colour index	68	0.9407 ± 0.0059	0.0484	66	0.9386 ± 0.0044	0.0360
Red blood corp., diameter	—	—	—	20	7.912 ± 0.013	0.041
H. v. d. Bergh	30	0.948 ± 0.060	0.330	36	0.756 ± 0.050	0.300
Serum iron	26	132.0 ± 7.0	35.9	21	103.8 ± 3.9	17.7

Table 10. *Differences between healthy men and healthy women from Umeå in regard to different laboratory figures.*

	Difference between men and women
Hb. in %	8.44 ± 1.01
RBC in millions	0.420 ± 0.054
S.r. in mm/hr	-2.27 ± 0.56
Colour index	0.0021 ± 0.0074
H. v. d. Bergh	0.192 ± 0.081
Serum iron	28.2 ± 8.0

A statistically significant difference is found to exist between men and women as regard Hb, red blood corpuscles, S.r. and serum iron but not as regards colour index or H. van den Bergh (serum bilirubin), although the difference between the sexes for serum bilirubin nearly reaches statistical probability. The serum bilirubin has been determined on the Upsala normal material, as by an oversight normal values for it were not determined on the Umeå material, on 30 healthy conscripts and 36 healthy nurses and Swedish ATS ('lottor') aged 20-40 years. Normal values for the diameter of the red blood corpuscles have been determined on 20 healthy nurses aged 20-30 years. In the Upsala normal material the males consist of 58 persons, mainly young soldiers, and the females of 64 nurses and ATS. As stated above, this material will be dealt with more fully in Chap. XII, but we shall here make a comparison between it and the Umeå normal material. The results are given in table 11.

Table 11. *Comparison between the normal cases from Umeå and the normal cases from Uppsala.*
 $M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation. $D \pm \epsilon(D)$ = difference between the means $\pm$ standard error of the difference.

Normal cases from Umeå		Normal cases from Uppsala			Diff.		
Num- ber	M + ε(M)	σ	Num- ber	M ± ε(M)	D ± ε(D)		
M e n							
Hb. in %	68	91.35 ± 0.76	6.29	58	104.09 ± 0.72	5.47	— 12.74 ± 1.05
Colour index	68	0.9407 ± 0.0059	0.048	58	1.00 ± 0.011	0.082	— 0.06 ± 0.012
RBC	68	4.844 ± 0.038	0.31	58	5.260 ± 0.056	0.42	— 0.42 ± 0.068
S.r. in mm/hr.	67	4.36 ± 0.40	3.28	58	3.40 ± 0.29	2.23	0.96 ± 0.49
W o m e n							
Hb. in %	66	82.91 ± 0.66	5.39	64	89.03 ± 0.84	6.71	— 6.12 ± 1.07
Colour index	66	0.9386 ± 0.0044	0.036	64	1.031 ± 0.012	0.098	— 0.09 ± 0.013
RBC	66	4.424 ± 0.039	0.31	64	4.344 ± 0.053	0.42	0.08 ± 0.066
S.r. in mm/hr.	64	6.63 ± 0.39	3.15	63	8.83 ± 0.55	4.35	2.20 ± 0.67

There are statistically significant differences for men as regards Hb, red blood corpuscles, and colour index, and for women as regards Hb, colour index and S.r. The S.r. can be left to side in the discussion. The observed statistical differences are primarily due to a personal error in the Hb readings, causing the Hb value in the Upsala material to be about 5 units higher than in the Umeå material. The significance of the personal recording error in the Hb determinations has been pointed out by Odin and Werdinius (1933). Largely speaking, it explains the difference for Hb and colour index in the female material, and for the colour index — though not for Hb and RBC — in the male, where there is reason to suppose that these latter values are higher, due to the daily vigorous physical exercises and the active open-air life of these young soldiers, that might drive the concentrated blood from their depots in the organism to the circulating blood, and perhaps the increased need of oxygen impel the blood forming organs to produce more haemoglobin and red blood corpuscles. These both mechanism may increase the values for Hb and RBC.

In this connection we may also cite Dahl's observation in 1944 that the values for Hb and red corpuscles often fall during a stay in hospital. The present author has investigated these matters on the males in the normal Umeå material, taking the values for Hb and red blood corpuscles on admission to and discharge from hospital. The results are given in the table 12.

Table 12. *The normal cases from Umeå. Differences between 2 determinations in regard to different laboratory figures in men.*

$D \pm \varepsilon(D)$ = Mean of the individual differences $\pm$ standard error of the mean; $\sigma(D)$ = standard deviation of the individual differences.

	Num- ber	M_1	M_2	$D \pm \varepsilon(D)$	$\sigma(D)$
Hb in %	38	92.3	89.3	3.0 ± 1.3	8.0
RBC in mill.	38	4.848	4.759	0.089 ± 0.068	0.420
Colour index	38	0.9524	0.9384	0.0139 ± 0.0078	0.0478

It is seen that there was a fall in Hb, red blood corpuscles and colour index during the stay in hospital, which in most cases lasted about 60 days. There are no statistically significant or probable differences between the values on admission and discharge, but it is possible that a larger material might give conclusive figures. The reason of this fall cannot be adduced from this material, but it may possibly be due to an agglomeration of concentrated blood in the depots of the organism (spleen, etc.).

Then comes the question whether regional conditions (in the one case in Northern Sweden, in the other Central Sweden) may have any bearing on the differences observed in the normal materials. According to the investigation of Odin and Werdi-
nius in 1933, the Norrland material showed lower Hb values than the Scanian (from southernmost Sweden). According to Enghoff's investigation of 1937, there were no differences either for Hb, red blood corpuscles, or haemotocrite between the Norrland and Upsala material, the Norrland and Scania material, or the Upsala and Scania material. On the other hand, there was a statistically significant difference as regards the diameter of the red blood corpuscles, measured by Bock's method, which was smaller in the Norrland material than in either of the others. We have therefore hardly any concrete reason for saying that environment has any material effect on the values for Hb and red blood corpuscles in our normal materials, except as to the diameter.

Survey of the pathological materials.

The materials to be dealt with here have been collected both from the sanatorium for rheumatic patients which is attached to the Central Hospital in Umeå, which part will hereafter be called the Umeå material, and from the Medical Clinic of the Academic Hospital in Upsala, hereafter called the Upsala material. The former was assembled during 1940-1943, and the latter during 1943-1945.

The Umeå material is the larger one, and is therefore intended to give a wider survey of the state of the blood in rheumatic

conditions of the type which in Sweden is usually called chronic rheumatic polyarthritis. This form of disease is nowadays generally acknowledged to be such as to attack the whole of the mesenchymal system. It must therefore be taken to include rheumatic tendinitis and polytendinitis, which complaints have been included in the material whether they were combined with polyarthritis or not. One case of spondylarthritis ankylopoetica has also been included. On the other hand, we have omitted cases of arthrosis only (e.g. *malum coxae senile* or arthrosis of the kneejoint), as also conditions of pain where neither case history nor status gave any evidence of arthritic or tendinitic rheumatic processes. If a case was doubtful, it was left out.

In this connection, it is impossible not to touch on the term 'rheumatoid arthritis'. Now, the aetiology of this form is not known, and this is surely the main reason why it is so difficult to generalise about this particular field. If we separate off the pure arthroses (arthritis deformans, osteoarthropathia deformans), there are many reasons for assuming an infectious or toxic aetiological factor in the remaining groups, particularly in those which begin acutely or have exacerbations with fever. (In certain cases, it has also been thought that hormonal influences are at work). The present author has sometimes used the expression 'infectious-toxic' to denote uncertainty with regard to the aetiology, but has often been content with the expression 'infectious'.

Without drawing any conclusions from it, it is impossible not to get the impression that there are many parallels between the different forms and types of course of, say, the tubercular disease and the rheumatic infection.

For simplicity's sake I shall, in the following pages, be using the term 'rheumatic infection' when I need a collective name for forms of rheumatic disease of infectious character.

Then comes the question whether rheumatic fever and the rheumatic infection tending to chronicity can be included in the same form of disease. Opinions are divided as to this. Those in favour of this being so seem commoner in German-speaking circles than in English-speaking ones, perhaps because rheumatic infectious run somewhat different courses in different

parts of the world. Moreover, rheumatic fever seems to cause chronic joint changes more often in Germany than in England (Kahlmeter). These groups have not been kept separate here. States following rheumatic fever are relatively few.

The Umeå material consists of 130 men and 207 women, receiving treatment one or more times during the years quoted. The investigation began on 1/1 1940, the methods having been tried out or checked, and the apparatus standardised, during 1939.

After the exclusion of cases on motives given above, further cases were weeded out, i.e. those where the patient was suffering from a disease or condition giving rise to such complications that the values for haemoglobin or the red blood corpuscles might be affected — for example, an infection which could not be considered to have any causal connection with the rheumatic complaint. Dental diseases and chronic tonsillitis did not seem cause for excluding cases from the material, not yet apparently cured lung tuberculosis or mild chronicising apical foci, which do not, to our knowledge, affect the blood values. Cases where there was pregnancy were left out. Cases with haemorrhage, whether in connection with a surgical operation or not were, unless the bleeding was very slight, also left out, and so were cases treated with sulfa preparations, and those treated with the gold preparation aurodetoxin. The present author has previously (1939) been able to show that this latter preparation induces anaemia. According to Sundelin's investigations of 1941, the gold component does not set up anaemia, and I, too, have subsequently found that the action inducing anaemia comes from the detoxin component: for this reason, cases treated with detoxin only have also been excluded (in all, 3 cases treated with aurodetoxin and detoxin). Cases with endocrine disturbances were excluded, and also cases with tapeworm. One case with injuries from arsenic dust has also been excluded.

Further, 15 girls and 5 boys, all under 18 years of age, were ruled out of the Umeå material. Unfortunately, this omission was not fully followed out in practice, so that 7 girls and 2 boys came to be included in the material. However, they are so few that they do not materially affect it.

The Upsala material was treated on the same principles, though this material includes cases of rheumatic fever (15 men and 12 women), and also 2 cases of Reiter's disease.

The grouping of the materials.

The materials were first of all divided up according to sex, and then according to domicile (country or town) and duration of the disease, into old and new cases. However, the town materials were small and were, in all essentials, the same as those from the country, so that these two groups were made into one. Statistical treatment according to the duration of the disease also proved not very expedient, since the new cases were comparatively few; for this reason this division was maintained only in some calculations, where it was thought to yield certain advantages. We also allowed for the fact that the rheumatic infections often proceed with acute exacerbations.

A survey is given to characterise the materials, first as regards the age both at the time the patient first fell ill and on admission to hospital.

Table 13. *The polyarthritic cases from Umeå and from Uppsala distributed according to age at the beginning of the illness.*

Age, years	Cases from Umeå				Cases from Uppsala			
	Men		Women		Men		Women	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
5—9	1	0.8	—	—	—	—	—	—
10—14	4	3.1	6	2.9	1	2.9	—	—
15—19	14	10.8	18	8.7	4	11.8	3	7.1
20—24	22	16.9	28	13.5	4	11.8	7	16.7
25—29	17	13.1	32	15.5	5	14.7	2	4.8
30—34	20	15.4	35	16.9	4	11.8	1	2.4
35—39	23	17.5	37	18.0	2	5.9	4	9.5
40—44	13	10.0	21	10.1	2	5.9	6	14.3
45—49	8	6.2	17	8.2	4	11.8	7	16.7
50—54	8	6.2	10	4.8	1	2.9	3	7.1
55—59	—	—	3	1.4	4	11.8	3	7.1
> 60	—	—	—	—	3	8.7	6	14.3
Total	130	100.0	207	100.0	34	100.0	42	100.0

Table 14. *The polyarthritic cases from Umeå and from Uppsala distributed according to age at admittance to hospital.*

Age, years	Cases from Umeå				Cases from Uppsala			
	Men		Women		Men		Women	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
10—14	1	0.8	0	0	—	—	—	—
15—19	3	2.3	13	6.3	7	17.1	4	7.1
20—24	20	15.4	25	12.1	4	9.8	4	7.1
25—29	16	12.3	27	13.0	6	14.6	4	7.1
30—34	19	14.6	27	13.0	4	9.8	1	1.8
35—39	25	19.3	32	15.5	1	2.4	2	3.6
40—44	19	14.6	34	16.4	3	7.3	2	3.6
45—49	16	12.3	26	12.6	4	9.8	6	10.7
50—54	9	6.9	18	8.7	1	2.4	9	16.2
55—59	2	1.5	5	2.4	5	12.2	6	10.7
> 60	—	—	—	—	6	14.6	18	32.1
Total	130	100.0	207	100.0	41	100.0	56	100.0

The Upsala material is older both as regards the age when the patient fell ill and when he or she was admitted to hospital: this undoubtedly has to do with the rules governing admission to the Royal Pensions Board's sanatoria.

An examination of the age at the last exacerbation (which examination is only feasible on the Umeå material) shows the median to fall at 36 years for both men and women. A survey of the duration between the last exacerbation and admission to hospital (also only possible on the Umeå material) shows the median for both men and women to fall between 1/2 and 3/4 of a year.

Table 15 gives data as to the duration of the disease from the first symptoms to admission to hospital.

Table 15. *The polyarthritic cases from Umeå and from Uppsala distributed according to duration of the illness (in years) before admittance to hospital.*

Years	Cases from Umeå				Cases from Uppsala			
	Men		Women		Men		Women	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0—½	20	15.4	27	13.1	23	69.8	22	49.0
½—1	10	7.7	44	21.4	4	12.1	4	8.9
1—2	21	16.2	22	10.6	1	3.0	1	2.2
2—3	18	13.8	21	10.1	—	—	3	6.7
3—4	11	8.5	18	8.7	1	3.0	3	6.7
4—5	10	7.7	12	5.8	1	3.0	2	4.4
5—6	9	6.9	16	7.7	—	—	—	—
6—7	3	2.3	8	3.9	—	—	2	4.4
7—8	1	0.8	3	1.4	—	—	—	—
8—9	2	1.5	10	4.8	—	—	2	4.4
9—10	1	0.8	4	1.9	—	—	1	2.2
> 10	24	18.4	22	10.6	3	9.1	5	11.1
Total	130	100.0	207	100.0	33	100.0	45	100.0

The cases in the Uppsala material are seen to show a perceptibly shorter duration, which undoubtedly links up with the fact that this material includes cases of acute polyarthritis, and that the Academic Hospital, takes in mainly acute cases, whereas the sanatorium in Umeå is specially arranged for the treatment of the disabling rheumatic diseases, tending to chronicity.

In the Umeå material, the period of treatment for the milder cases averaged 60 days. For the medium cases, the usual period was 60—90 days, and for the severe cases up to 120 days. The period of treatment varied more in the Uppsala material; a certain number of cases were only examined once, and then usually in the Out-Patients' Department.

The materials were also divided up according to type of course before admission and joint status on admission and discharge respectively, together with the course of the disease between admission and discharge.

Three groups have been drawn up for the *type of course* (by which is meant the course just before admission): A, B, and C. They are based on the case history.

Group A implies an improvement in the condition, or stationary condition. Group B implies a slow progress of the disease, and Group C a more rapid progress possibly with fever.

Groups D, E, and F have been drawn up to show *joint status* on admission and discharge; these are based on data from the status. Group D contains cases with only subjective symptoms (arthritisms), milder productive forms (e.g. cases with only Heberden's nodules and aftermaths, without any very marked activity or tendency to progression); E and F contain the cases of active rheumatoid arthritis. Group F has been made to cover the cases where there is fever, or exudation in one or more joints — provided that the exudate does not spring from another cause than activity in the joint process, such as joint mouse, deforming changes in the joint, or the like. All other cases are relegated to group E.

Using the joint status at admission and discharge as guide, the course between admission and discharge (result of treatment) has been classified under groups a, b, and c (improved, no improvement, worse). The joint status has been taken from the charts of the original journals, where every joint available for investigation has been described by a sign denoting respectively spontaneous pain, pain on moving, crepitation, capsular swelling and exudation, and transferred to the statistical treatment card, where subjective symptoms are shown by +, capsular swelling by ++ and exudation by +++.

The table 16 shows the number of cases in each group in both materials.

Table 16. *The polyarthritic cases from Umeå and from Uppsala distributed according to type of course before admittance, joint status at admittance, joint status at discharge and the course between admittance and discharge.*

Type, status or course	Type of course before admittance		Joint status at admittance		Joint status at discharge		Course between admittance and discharge	
	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Men from Umeå								
best	82	63.1	49	37.7	62	47.8	82	63.0
medium	39	30.0	52	40.0	47	36.1	43	33.1
worst	9	6.9	29	22.3	21	16.1	5	3.9
Total	130	100.0	130	100.0	130	100.0	130	100.0
Women from Umeå								
best	101	48.8	56	27.1	81	39.1	123	59.4
medium	89	43.0	109	52.6	93	45.0	72	34.8
worst	17	8.2	42	20.3	33	15.9	12	5.8
Total	207	100.0	207	100.0	207	100.0	207	100.0
Men from Uppsala								
best	14	34.2	12	29.3	17	51.5	27	81.8
medium	13	31.6	14	34.1	10	30.3	4	12.1
worst	14	34.2	15	36.6	6	18.2	2	6.1
Total	41	100.0	41	100.0	33	100.0	33	100.0
Women from Uppsala								
best	17	30.4	7	12.5	14	46.7	16	48.5
medium	20	35.7	40	71.4	13	43.3	16	48.5
worst	19	33.9	9	16.1	3	10.0	1	3.0
Total	56	100.0	56	100.0	30	100.0	33	100.0

It is plain that this division of articular cases is, to a certain extent, not hard and fast. The data in the case history have their inaccuracies, and all joints are not accessible to investigation. However, the way we have chosen seems to be the most

practicable one, and appears to correspond fairly well to different degrees of activity in the disease, and this also reflects the principle behind the division: namely, to collect the articular cases into different activity groups, since one has the impression that the anaemias associated with the basis disease become more severe, the more active the disease is.

The type of course before admission can be taken to denote the actual progressive tendency of the disease, and the joint status group its actual activity. However, these principles of division do not give the same grouping of the material, due to the fact that a fairly mild case of polyarthritis can show a strong progressive tendency, while a more severe case may show a more stationary condition.

Determinations of Hb, red blood corpuscles, S.r. and colour index were frequently made during the period of treatment in the whole of the Umeå material and most of the Upsala material. In certain parts of the former, the diameter of the red corpuscles was measured, the reticulocytes counted, and the serum bilirubin, serum iron, and urobilin and urobilinogen in the urine determined once or more during the period of treatment; in addition, peroral iron loadings were carried out and, in certain cases, iron loading before and after iron treatment. Ewald's test meal was given in a large number of cases. Epithelial symptoms were observed. The temperatures have been quoted. Some of the cases received iron treatment, and here the preparation and period of treatment are given. The physical therapy was recorded, and also any other therapy of importance. Besides this, some of the Upsala material were loaded with iron by intravenous injection. Copper determinations in the serum were carried out. Haemotocrite determinations were made, and the absolute figures for the relation between red blood corpuscles and Hb calculated, for the whole of the Upsala material.

Separate data will be found in the chapters dealing with the special questions.

CHAPTER V.

Rheumatoid symptoms in regard to the blood;
the frequency of anaemia and the question
of correction of S.r. for anaemia.

Comparison between the normal Umeå material
and the total pathological Umeå material.

The normal material has already been described in Chapter IV. The table 17 outlines the pathological Umeå material, 130 men and 207 women, which is described more fully in Chapter IV.

Table 17. *Different laboratory figures in polyarthritic cases
from Umeå.*

$\bar{M} \pm \varepsilon(\bar{M})$ = Mean $\pm$ standard error of the mean; σ = standard deviation.

	M e n			W o m e n		
	Num- ber	$\bar{M} \pm \varepsilon(\bar{M})$	σ	Num- ber	$\bar{M} \pm \varepsilon(\bar{M})$	σ
Hemoglobin	130	86.64 ± 0.89	10.10	207	75.23 ± 0.61	8.76
Red blood corpuscles	130	4.708 ± 0.041	0.465	207	4.245 ± 0.024	0.338
Sedimentation rate	130	20.9 ± 2.0	23.1	207	23.0 ± 1.4	19.6
Colour index	130	0.9218 ± 0.0061	0.0695	207	0.8869 ± 0.0055	0.0785
Reticulocytes	15	4.5 ± 1.0	3.9	33	7.8 ± 1.0	5.8
Red blood corp. diameter	16	7.719 ± 0.026	0.103	33	7.661 ± 0.046	0.264
H. v. d. Bergh	90	0.851 ± 0.049	0.463	130	0.740 ± 0.027	0.310
Serum iron	80	96.1 ± 4.8	42.7	129	74.7 ± 2.9	33.4

The difference between men and women in the pathological material is shown in the table 18. There is a statistically significant difference for Hb, RBC, colour index, and serum iron.

Table 18. *Difference between different laboratory figures in polyarthritic men and women from Umeå.*

	Difference men — women
Hemoglobin	11.41 ± 1.08
Red blood corpuscles	0.463 ± 0.048
Sedimentation rate	-2.1 ± 2.4
Colour index	0.0349 ± 0.0082
Reticulocytes	-3.3 ± 1.4
Red blood corp., diameter	0.058 ± 0.053
H. v. d. Bergh	0.111 ± 0.056
Serum iron	21.4 ± 5.6

It will perhaps be more interesting to compare the normal material with the total pathological material; this is done in the table 19.

Table 19. *Difference between laboratory figures in healthy and polyarthritic men and women from Umeå.*

	Diff. healthy cases — polyarthritic cases	
	M e n	W o m e n
Hemoglobin	4.71 ± 1.17	7.68 ± 0.90
Red blood corpuscles	0.136 ± 0.056	0.179 ± 0.046
Sedimentation rate	-16.55 ± 2.07	-16.35 ± 1.41
Colour index	0.0189 ± 0.0085	0.0517 ± 0.0070
Red blood corp., diameter	0.193 ± 0.029	0.251 ± 0.048
H. v. d. Bergh	0.097 ± 0.077	0.016 ± 0.057
Serum iron	35.9 ± 8.5	29.1 ± 4.9

Here there are statistically significant differences for men and women as regards Hb, S.r., serum iron and diameter; and, for women, for RBC and colour index also.

The men, that is to say, have fewer statistically significant differences. This may be because they include more mild cases, or because their blood shows a greater resistance to the rheumatic toxins. These matters will also be discussed further when the various groups of material are examined.

As might be expected, there is a considerably greater dispersion round the medium in the pathological material than in the normal; this is particularly so in the case of Hb and S.r. both for men and women, but there is also a greater dispersion for red blood corpuscles and colour index in the pathological material. This greater dispersion is due to the lower values found in the latter material. They also cause the average of the normal and the pathological material to be declined, so that it is lower for the pathological material. The difference between the two materials is statistically significant for Hb and S.r. both for men and women, and for red blood corpuscles and colour index for women, while in men it is only probable for these two last. The anaemia frequency is greater in women than in men. The reason cannot be deduced from the table, but we know from experience that women suffer from anaemia more often than men. This is particularly true in the case of hypochromic anaemias, and is probably connected to a certain extent with the periodic loss of blood due to menstruation and pregnancy. In any case women have lower normal values than men. If they are assessed according to the same norms, they will accordingly appear to have milder forms of anaemia. It cannot be determined here whether the female blood apparatus is more sensitive to the harmful influence exerted by the rheumatic infection, or whether it is that more serious cases are included among the women. Be that as it may, rheumatoid arthritis is far commoner among women than among men. The sedimentation rate argues however, against this, both in that the women show almost the same difference as the men when compared with the normal material, and in that, when ill, they are not more so than the men. As will be shown later, there is a correlation between the Hb values and the S.r. Thus, the circumstance which has been pointed out would seem

in the first place to suggest the same sensitivity in the women to the injurious factor.

The fact that the women, but *not* the men, show a significant difference between the colour indices in pathological and normal material respectively may possibly be due to chance. The differences of the two sexes differ by $0.03 \pm 0.0107\%$ — i.e. a difference not altogether statistically significant, though very probable. It is possible that women are more prone to hypochromic or microcytic anaemia than men. This is the case in a normal population, and it would be natural to find the same tendency in rheumatic subjects. Waldenström's and Lundholm's investigations have shown us that country populations suffers from hypochromic anaemia more often than town populations. Our materials have been taken from one and the same district, and cover about the same proportion of town and country dwellers. The normal material should therefore be perfectly comparable with the pathological material. Now, it is not clear how far iron deficiency in the diet contributes to cause hypochromic anaemia. It is probably a fact that hereditary factors play a part, as also iron losses, due to menstruation and pregnancy. It is difficult to decide which of these factors may have been mainly responsible for the probable difference we found between men and women as regards the make-up of their blood. Some indication that the women are more sensitive to the rheumatic agent than the men is found in a circumstance that will be touched on later — namely, that women are far more liable to epithelial symptoms during a rheumatic infection than men are.

The effect of different factors on the state of the haemoglobin and red corpuscles in the blood.

Here, too, it is worth mentioning that *only* infectious cases are included in the arthritis material, the osteo-arthritis cases being left out. The material has been divided into sexes, and contains 130 men and 207 women. One of the female cases provides no data as to the number of red blood corpuscles.

All the values given here are those obtained on admission to hospital.

Comparison between the Umeå normal material and the total Umeå pathological material was made and discussed in the previous chapter.

Before proceeding to examine the anaemia frequency in this arthritis material, I have therefore divided it up according to data from the case history, primarily with regard to the duration of the disease before admission. The dividing-line has been drawn at 2 years, so that the one group contains cases where the case history reports the disease to have lasted 2 years or less before admission to hospital, and the other where it has lasted more than 2 years. Only values for Hb and red blood corpuscles have been included in this tabulation. Men and women have been classified separately. At first we present the *male* material. See Table 20.

Table 20. *Figures of Hb and RBC in different groups of the polyarthritic material from Umeå. Distribution according to case history. Men.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Groups	Hemoglobin values in %			Red blood corpuscles in millions		
	Num-ber	$M \pm \varepsilon(M)$	σ	Num-ber	$M \pm \varepsilon(M)$	σ
X. Distribution of the material with regard to duration of the illness before admittance.						
2 years	61	85.97 ± 1.31	10.2	61	4.732 ± 0.062	0.49
> 2 years	69	87.23 ± 1.20	9.9	69	4.685 ± 0.053	0.44
Diff.		-1.26 ± 1.78			$+ 0.047 \pm 0.082$	
Y. Distribution of the material with regard to the interval between the last exacerbation and admittance.						
$< \frac{1}{2}$ year	17	79.47 ± 1.91	7.9	17	4.342 ± 0.069	0.29
$> \frac{1}{2}$ year	26	86.77 ± 2.07	10.6	26	4.623 ± 0.086	0.44
Diff.		-7.30 ± 2.82			-0.281 ± 0.110	
Z. Distribution of the material with regard to type of course before admittance.						
A	82	89.63 ± 0.98	8.9	82	4.834 ± 0.049	0.44
B	39	83.26 ± 1.61	10.0	39	4.524 ± 0.071	0.44
C	9	74.00	—	9	4.352	—
Diff. A—B		$+ 6.37 \pm 1.88$			$+ 0.310 \pm 0.086$	

Division of the male material with regard to the duration of the disease yields no statistically significant difference between the time groups mentioned in X Table 20.

Those who have been in the position to observe cases of rheumatic infection for any length of time know very well that this form of disease has a pronounced tendency to proceed in exacerbations more or less severe, sometimes manifesting themselves as a subjective turn for the worse with increased aching, pain in moving, and stiffness in the joints, and sometimes with more marked objective signs of deterioration in the form of fever, increased swelling and perhaps exudation in the joints. Anamnestic data have made it possible to date this kind of exacerbation of the joint disease in 43 cases of arthritis. see Y in Table 20.

The material has been divided into 2 groups, one containing those cases where the period between the beginning of the exacerbation and admission to hospital was half a year or less, and the other where this period was longer than half a year. It is found that the difference between these groups is, statistically, very probable both for Hb and red blood corpuscles: this means that in all likelihood, the exacerbation of the disease had an impairing effect on the patient's blood values for Hb and red blood corpuscles.

The material has also been classified according to the type of the course before admission. No differentiation was made between cases with and without exacerbations respectively. The type of the course during the last half year decided the placing of the case. The material has been divided into 3 groups. Group A contains cases where the course before admission showed a stationary state or improvement in a lesser or higher degree, group B contains the cases where the disease progressed slowly, and group C the cases progressing more rapidly, possibly with fever. It is clear that these groups cannot be altogether clear-cut, but it has been possible to divide them up on these principles. The material is presented in Z Table 20.

This shows that group A is unquestionably the largest. There, too, the values for Hb and red blood corpuscles are highest, higher than in the total material. The difference as

compared with group B (slowly progressing cases) is statistically significant both for Hb and red blood corpuscles, indicating that the progressive tendency of the cases constitutes an anaemising factor. The cases in group C emphasise this still further. No statistical calculation has been made on the cases in group C, as they are so few, only 9 in number, but they have 15 % lower Hb and about a half million fewer red blood corpuscles than those in group A.

For the *female* cases, the same investigation has been made into the anaemia frequency in different groups, in the light of data from the case history, and the results are given in Table 21, where the sub-divisions X, Y and Z are included.

Table 21. *Figures of Hb and RBC in different groups of the material from Umeå. Distribution according to case history. Women.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation

Groups	Hemoglobin values in %			Red blood corpuscles in millions		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
X. Distribution of the material with regard to duration of the illness before admittance.						
< 2 years	102	76.83 ± 0.82	8.3	102	4.279 ± 0.033	0.33
> 2 years	105	73.68 ± 0.87	8.9	105	4.212 ± 0.033	0.34
Diff.:		$+ 3.15 \pm 1.20$			$+ 0.067 \pm 0.047$	
Y. Distribution of the material with regard to the interval between the last exacerbation and admittance.						
< $\frac{1}{2}$ year	33	74.03 ± 1.52	8.7	33	4.205 ± 0.054	0.31
> $\frac{1}{2}$ year	48	74.17 ± 1.32	9.1	48	4.201 ± 0.058	0.40
Diff.:		$- 0.14 \pm 2.01$			$+ 0.004 \pm 0.079$	
Z. Distribution of the material with regard to type of course before admittance.						
A	101	77.56 ± 0.86	8.6	101	4.301 ± 0.033	0.33
B	89	74.00 ± 0.85	8.0	89	4.224 ± 0.035	0.33
C	17	67.82 ± 1.97	8.1	17	4.024 ± 0.084	0.35
Diff.: A—B		$+ 3.56 \pm 1.21$			$+ 0.077 \pm 0.048$	
» A—C		$+ 9.74 \pm 2.15$			$+ 0.277 \pm 0.090$	
B—C		$+ 6.18 \pm 2.15$			$+ 0.200 \pm 0.091$	

A probable difference is found, since the women who had been suffering from rheumatic infections for more than 2 years have a higher degree of anaemia than those suffering for 2 years or less. See group X in Table 21. This may be due to chance, but, may be because the intermediary metabolism of the women is more vulnerable, which in its turn may be due to their periods losses of iron. It is of course conceivable that they may be more sensitive to the rheumatic toxin for other reasons, also. Unlike the results found among the men, there is no statistically demonstrable difference if the material is studied with regard to the interval between the last exacerbation and admission.

As with the men, the groups show more perceptible differences if the material is studied according to the type of the course before admission. Here, too, the groups are larger because, as is usual with rheumatic arthritis, the female material is larger. The difference is probable for Hb if consecutive groups are compared, and significant both for Hb and red blood corpuscles if groups A and C are compared.

Proceeding to study the state of the blood in different sections according to reports from the status of the men, the first task will be to investigate the anaemia frequency in different groups of joint status, here called D, E and F.

Group D contains the cases only presenting subjective symptoms, among which the so-called arthritisms have been included. This group has also been made to cover cases with fairly slight productive changes (e.g. only Heberden's nodes), and aftermaths of polyarthritis without distinct activity or progressive tendency, and with slight objective symptoms. Groups E and F contain the cases with objective symptoms, with the above-mentioned exceptions. It would be correct to assume that these groups include the active, more severe rheumatic infections. Group F covers the cases attended by fever, and those where there is exudation in the joints and increased heat above the joints, provided, that is to say, that the exudate cannot be attributed to causes other than the rheumatic infection, such as joint mouse, deforming changes in the joint, or the like. All other cases have been relegated to group E. It is

worth mentioning that the status of the joints has been entered on charts by physicians experienced in the investigation technique of rheumatology with a system of signs for different joint symptoms.

It is plain that this division according to joint status need not be a hard-and-fast expression of the activity of the process: an older form of polyarthritis with lowered activity may very well present a more serious joint status than a more recent case with considerably higher activity. Here, too, there are of course boundary-line cases between the different groups, which are difficult to place.

Table 22. *Figures of Hb and RBC in different groups of the polyarthritic material at admittance to the hospital.*

Men from Umeå.

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation.

Groups	Hemoglobin figures in %			Red blood corpuscles in millions		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
X. Distribution of the material with regard to the status of the joints at admittance.						
D	49	90.69 ± 1.25	8.7	49	4.857 ± 0.061	0.42
E	52	86.77 ± 1.34	9.7	52	4.711 ± 0.065	0.47
F	29	79.55 ± 1.74	9.4	29	4.449 ± 0.079	0.42
Diff.: { D—E		$+ 3.92 \pm 1.83$			$+ 0.146 \pm 0.089$	
{ D—F		$+ 11.14 \pm 2.14$			$+ 0.408 \pm 0.100$	
{ E—F		$+ 7.22 \pm 2.20$			$+ 0.262 \pm 0.102$	
Y. Distribution of the material with regard to S.r. at admittance.						
≤ 5 mm/hr	41	90.78 ± 1.49	9.5	41	4.863 ± 0.071	0.45
> 5 mm/hr	89	84.73 ± 1.04	9.8	89	4.636 ± 0.048	0.45
Diff.:		$+ 6.05 \pm 1.82$			$+ 0.277 \pm 0.086$	
Z. Distribution of the material with regard to morning temperature at admittance.						
$\leq 37^\circ$	120	87.76 ± 0.86	9.4	120	4.744 ± 0.041	0.45
$> 37^\circ$	10	73.20 ± 2.63	8.3	10	4.275 ± 0.136	0.43
Diff.,		$+ 14.56 \pm 2.77$			$+ 0.469 \pm 0.142$	

It is seen in X in Table 22 that the anaemia frequency shows a successive rise, with the highest value in group F, and with the greatest difference between groups E and F. The difference between groups D and E both for Hb and red blood corpuscles may be due to chance; between D and F, however, it is statistically significant for both, and between E and F statistically significant for Hb, and probable for red blood corpuscles.

If, as mentioned above, the joint status cannot in all cases be taken as a trustworthy gauge of the degree of actual activity of the rheumatic process, there is reason to assume that the height of the S.r. and the temperature are sure signs of activity in the process, in that fever and raised S.r. show the rheumatic infection to be active.

A tabulation of the sedimentation rate gives the following results. See Y in Table 22.

A sedimentation rate of the blood corpuscles of 5 mm/hour and less has been considered normal for men. There is then a statistically significant difference for both Hb and red blood corpuscles between this normal group and the cases with a sedimentation rate of more than 5 mm/hour.

The material has furthermore been divided up, according to the morning temperature on admission to hospital, into non-febrile and febrile cases. The limit has been set between 37°C . and under, and above 37°C . Among the men, 10 cases had a morning temperature of more than 37° , and these 10 showed 14 % lower Hb than the 120 non-febrile cases; the difference is statistically significant. A difference of this kind also obtains for the red blood corpuscles. See Z in Table 22.

Studying the material of *female* polyarthritics in the same way, we again find falling values both for Hb and red blood corpuscles in the different groups, according as there are more objective symptoms from the joints. Here, however, there is a statistically significant difference for Hb only for groups D-F, and a statistically probable difference for the groups E-F. There is no statistically significant or probable difference for the red blood corpuscles. The reason may be the same as that stated when discussing the total material for women, namely, that women are more liable than men to hypochromia or

microcytosis from the rheumatic toxin (tendency to chlorosis or iron deficiency anaemia? which is characterised by undiminished number of red blood corpuscles). See X in Table 23.

Table 23. *Figures of Hb and RBC in different groups of the polyarthritic material at admittance to the hospital.*

Women from Umeå.

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Groups	Hemoglobin figures in %			Red blood corpuscles in millions		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
X. Distribution of the material with regard to status of the joints at admittance.						
D	56	78.43 ± 1.16	8.7	56	4.267 ± 0.048	0.36
E	109	75.22 ± 0.81	8.5	109	4.262 ± 0.030	0.32
F	42	71.00 ± 1.20	7.8	42	4.172 ± 0.055	0.36
Diff.: D—E		$+ 3.21 \pm 1.41$			$+ 0.005 \pm 0.057$	
Diff.: D—F		$+ 7.43 \pm 1.67$			$+ 0.095 \pm 0.073$	
Diff.: E—F		$+ 4.22 \pm 1.45$			$+ 0.090 \pm 0.063$	
Y. Distribution of the material with regard to S.r. in mm/hr at admittance.						
≤ 12	81	77.00 ± 0.95	8.5	81	4.293 ± 0.037	0.34
> 12	126	74.10 ± 0.78	8.7	126	4.214 ± 0.030	0.33
Diff.:		$+ 2.90 \pm 1.23$			$+ 0.079 \pm 0.048$	
Z. Distribution of the material with regard to morning temperature at admittance.						
$< 37^\circ$	181	75.88 ± 0.64	8.6	181	4.254 ± 0.026	0.35
$> 37^\circ$	26	70.73 ± 1.75	8.9	26	4.180 ± 0.052	0.27
Diff.:		$+ 5.15 \pm 1.86$			$+ 0.074 \pm 0.058$	

We now proceed to the sedimentation rate among the women, putting the limit for the normal at 12 mm/hour. The values are set out in Y in Table 23.

The table shows that there is no statistically significant or probable difference.

Z in Table 23 in which the female material is divided up according to the temperature on admission, shows a statistically

probably difference as regards Hb between non-febrile and febrile cases. The discrepancy between male and female cases may be due to the fact that some cases with premenstrual rise of temperature have crept into the female material.

We saw that there was no statistically significant or probable difference, when dividing the female material in groups < 12 and > 12 mm/hour. This may be because the limit for normal S.r. was set too low. The result of placing it at 20 mm/hour is shown in Table 24. We now find a statistically significant difference as regards Hb, but not as regards the red blood corpuscles.

If the limit is raised to 30 mm/hour, we get a statistically significant difference for Hb, and a statistically probable difference for the red blood corpuscles.

Table 24. *Comparison between hemoglobin and RBC figures in polyarthritic women from Umeå with different sedimentation rate.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation.

	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ	Diff.
	S.r. < 20			S.r. > 20 mm/hr			
Hb	114	77.50 ± 0.81	8.7	93	72.45 ± 0.83	8.0	+ 5.05 ± 1.16
RBC	114	4.291 ± 0.032	0.34	93	4.189 ± 0.034	0.33	+ 0.102 ± 0.047
	S.r. < 30			S.r. > 30 mm/hr			
Hb	158	76.44 ± 0.67	8.5	49	71.35 ± 1.24	8.7	+ 5.09 ± 1.41
RBC	158	4.281 ± 0.026	0.32	49	4.128 ± 0.051	0.36	+ 0.153 ± 0.057

The effect of different factors on the blood as reflected in colour index, sedimentation rate, and serum bilirubin.

The behaviour of the colour index in the total pathological material as compared with that in the normal material has already been dealt with in the previous chapter, where it was found that there was a statistically probable difference for men and a significant difference for women. This was discussed in the same chapter.

The serum bilirubin in the normal material and the total Umeå material of polyarthritics was treated in Chap. IV, where it was found that there was no statistically significant or probable difference between the sexes either in the normal material or the total Umeå material; nor did either the men or the women in both materials show any such differences. The difference between the sexes in the normal material is more than statistically probable, however ($2\frac{1}{2}$ the standard error of the difference was 0.203, and the difference between the means for men and women was 0.192).

Our task here is to investigate how different factors (type of course, joint status, fever, and S.r.) affect the colour index, sedimentation rate, and serum bilirubin. A table has also been made to show the colour index and the serum bilirubin in anaemic and nonanaemic cases respectively.

Table 25. *Colour index and H. v. d. Bergh in the polyarthritic material from Umeå when divided according to different types of course before admittance.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Course of illness before admittance	Men			Women		
	Num-ber	$M \pm \varepsilon(M)$	σ	Num-ber	$M \pm \varepsilon(M)$	σ
Colour index						
A	82	0.9293 ± 0.0067	0.0611	101	0.9025 ± 0.0077	0.0772
B	39	0.9215 ± 0.0119	0.0746	89	0.8779 ± 0.0079	0.0741
C	9	0.8556	—	17	0.8418 ± 0.0210	0.0864
B+C	48	0.9092 ± 0.0117	0.0813	106	0.8721 ± 0.0075	0.0769
H. v. d. Bergh						
A	50	0.981 ± 0.076	0.540	53	0.842 ± 0.051	0.374
B	31	0.713 ± 0.056	0.309	64	0.683 ± 0.030	0.241
C	9	0.606	—	13	0.612 ± 0.051	0.185
B+C	40	0.689 ± 0.045	0.283	77	0.671 ± 0.027	0.233

Differences between colour index and H. v. d. Bergh in different groups the material when divided to types of course before admittance.

	M e n	W o m e n
	Colour index	
A—B	0.0078 ± 0.0137	0.0246 ± 0.0110
A—C	—	0.0607 ± 0.0224
B—C	—	0.0361 ± 0.0224
A—(B+C)	0.0201 ± 0.0135	0.0304 ± 0.0107
	H. v. d. Bergh	
A—B	0.268 ± 0.094	0.159 ± 0.059
A—C	—	0.230 ± 0.072
B—C	—	0.071 ± 0.059
A—(B+C)	0.292 ± 0.088	0.171 ± 0.058

As regards colour index in Table 25 the men show no statistically significant or probable difference between the groups for the type of course; on the other hand, there is a statistically probable difference between these groups for the women. This holds both if the best (A) and the worst (C) groups is compared, and also if a comparison is made between the best group and the two less good groups made into one (B + C).

For serum bilirubin, determined according to H. van den Bergh's method, there is for the men a statistically probable difference between groups A and B, and a statistically significant difference between A and B + C, whereas for the women, where the material is larger, there are statistically probable differences between A and B and between A and B + C, and a significant difference between A and C. These circumstances call for special discussion.

The table 26 shows the colour index and serum bilirubin in relation to different joint statuses; the S.r. is also included. The difference for S.r. is always significant, no matter what the joint status group.

Table 26. *Different laboratory figures in patients from Umeå in groups with different status of the joints.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Joint status groups	Men			Women			Diff. between different joint status groups		
	Number	$M \pm \varepsilon(M)$	σ	Number	$M \pm \varepsilon(M)$	σ	Groups	Men	Women
Sedimentation rate, mm.									
D	49	8.6 ± 1.4	9.7	56	11.61 ± 0.99	7.41	D—E	-10.3 ± 2.9	-10.78 ± 1.90
E	52	18.9 ± 2.5	17.8	109	22.39 ± 1.62	16.98	D—F	-36.7 ± 5.6	-28.03 ± 4.03
D+E	101	13.9 ± 1.5	15.3	165	18.73 ± 1.19	15.34	(D+E)—F	-31.4 ± 5.6	-20.91 ± 4.09
F	29	45.3 ± 5.4	29.1	42	39.64 ± 3.91	25.36	F—F	-26.4 ± 6.0	-17.25 ± 4.23
Colour index.									
D	49	0.9338 ± 0.0093	0.0652	56	0.9195 ± 0.0087	0.0651	D—E	$+0.0123 \pm 0.0121$	$+0.0370 \pm 0.0114$
E	52	0.9215 ± 0.0077	0.0558	109	0.8825 ± 0.0073	0.0765	D—F	$+0.0317 \pm 0.0196$	$+0.0645 \pm 0.0158$
D+E	101	0.9275 ± 0.0060	0.0605	165	0.8950 ± 0.0058	0.0749	(D+E)—F	$+0.0254 \pm 0.0183$	$+0.0400 \pm 0.0144$
F	29	0.9021 ± 0.0173	0.0934	42	0.8550 ± 0.0132	0.0852	E—F	$+0.0317 \pm 0.0196$	$+0.0275 \pm 0.0151$
H. v. d. Bergh									
D	28	0.979 ± 0.098	0.520	18	0.928 ± 0.121	0.514	D—E	$+0.168 \pm 0.115$	$+0.182 \pm 0.125$
E	36	0.811 ± 0.061	0.396	73	0.746 ± 0.033	0.281	D—F	$+0.210 \pm 0.140$	$+0.284 \pm 0.124$
D+E	64	0.884 ± 0.055	0.442	91	0.782 ± 0.036	0.343	(D+E)—F	$+0.115 \pm 0.114$	$+0.138 \pm 0.045$
F	26	0.769 ± 0.100	0.511	39	0.644 ± 0.029	0.180	E—F	$+0.042 \pm 0.117$	$+0.102 \pm 0.044$

As regards colour index, the women show statistically significant differences between D and E, and D and F, and a probable difference between D + E and F; for serum bilirubin, they show a probable difference between D + E and F. Otherwise, there are no probable or significant differences between the joint status groups, either for men or women, though the values show there is a tendency towards lower serum bilirubin in the worse cases.

There are no statistically probably or significant differences for colour index and serum bilirubin between febrile and non-febrile cases, although the difference for the colour index in the women is very nearly $2\frac{1}{2}$ times its standard error. The male material is too small to give any definite results, and as has been pointed out earlier, even the female results may easily have been influenced by a premenstrual rise in temperature in some of the subjects. Therefore we do not publish the figures.

Investigating the colour index and serum bilirubin in relation to an S.r. of respectively ≤ 10 and > 10 mm/1h for men, and ≤ 30 and > 30 mm/1h for women, we find a statistically significant difference for serum bilirubin among the women.

The values for colour index and serum bilirubin in non anaemic and anaemic cases (the latter arranged with 2 different limits: the normal mean for Hb diminished with one σ and two σ) are tabulated in tables 28.

The colour index shows throughout statistically significant differences for both men and women, no matter which groups are compared. For the men, as regards serum bilirubin, there are significant differences between groups III and I, and III and I + II, and a probable difference between III and II but not between II and I. The women show no statistically significant or probable differences, although there is perceptible tendency towards lower serum bilirubin values with lower values for Hb and red blood corpuscles. It is impossible to say with certainty what causes this difference between men and women in this respect. The serum bilirubin values are always lower in women, even in normal cases. Is there perhaps some 'braking' mechanism which prevents the values from falling indefinitely?

Table 27. *Colour index and H. v. d. Bergh with regard to S.r.*
 $M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	S. r.						Diff.
	< 10 ♂ < 30 ♀			> 10 ♂ > 30 ♀			
	num- ber	$M \pm \epsilon(M)$	σ	num- ber	$M \pm \epsilon(M)$	σ	
Colour index	64	0.9358 ± 0.0077	0.0613	66	0.9083 ± 0.0091	0.0742	0.0275 ± 0.0119
H. v. d. Bergh	32	0.909 ± 0.061	0.343	58	0.819 ± 0.068	0.516	0.090 ± 0.091
			W o m e n				
Colour index	158	0.8932 ± 0.0061	0.0766	49	0.8667 ± 0.0117	0.0819	0.0265 ± 0.0132
H. v. d. Bergh	87	0.791 ± 0.036	0.332	43	0.638 ± 0.035	0.231	0.153 ± 0.050

Table 28. *Different laboratory figures in anemic and not anemic patients from Umeå.*M $\pm$ ϵ (M) = mean $\pm$ standard error of the mean, σ = standard deviation.

Hb	Colour index			H. v. d. Bergh		
	Num- ber	M $\pm$ ϵ (M)	σ	Num- ber	M $\pm$ ϵ (M)	σ
M e n						
$\leq 74 = \text{I}$	15	0.8227 ± 0.0248	0.0959	14	0.636 ± 0.049	0.184
75—84 = II	39	0.9072 ± 0.0089	0.0558	26	0.713 ± 0.056	0.283
I + II	54	0.8837 ± 0.0105	0.0775	40	0.686 ± 0.040	0.253
$> 85 = \text{III}$	76	0.9489 ± 0.0054	0.0472	50	0.983 ± 0.078	0.550
Diff.: III—I		0.1262 ± 0.0254			0.347 ± 0.092	
Diff.: III—II		0.0417 ± 0.0104			0.270 ± 0.096	
Diff.: II—I		0.0845 ± 0.0263			0.077 ± 0.074	
Diff.: III—(I+II)		0.0652 ± 0.0118			0.297 ± 0.088	
W o m e n						
$\leq 69 = \text{I}$	47	0.8047 ± 0.0119	0.0817	34	0.660 ± 0.049	0.286
70—79 = II	83	0.8830 ± 0.0065	0.0591	50	0.745 ± 0.039	0.277
I + II	130	0.8547 ± 0.0068	0.0775	84	0.711 ± 0.031	0.280
$> 80 = \text{III}$	77	0.9413 ± 0.0047	0.0416	46	0.795 ± 0.052	0.355
Diff.: III—I		0.1366 ± 0.0128			0.135 ± 0.071	
Diff.: III—II		0.0583 ± 0.0080			0.050 ± 0.065	
Diff.: II—I		0.0783 ± 0.0136			0.085 ± 0.063	
Diff.: III—(I+II)		0.0866 ± 0.0083			0.084 ± 0.061	

As was mentioned in the chapter on methods, these investigations of the serum bilirubin were carried out with H. van den Bergh's method, not using the modifications which were proposed by Thannhauser and Andersen (1921) and also by Jendrassik and Cleghorn (1936) with a view to prevent the binding of the bilirubin to the precipitated serum protein. Comparative investigations have shown that the original method gives lower values than the modified one but it is also said (Vahlquist 1941) that figures got with the original method are too inexact to be compared with one another. We have therefore carried out a comparative study on 30 normal persons (conscripts) with the original method, the modified method, and the icterus index according to Meulengracht. See the following table.

H. van den Bergh (original method)	Icterus index (Meulengracht)	H. van den Bergh (Jendrassik and Cleghorn)
0.424 ± 0.030 $\sigma = 0.165$	3.53 ± 0.21 $\sigma = 1.17$	0.666 ± 0.033 $\sigma = 0.183$

The values for H. van den Bergh are here given in mgm %. As is seen, the values are higher in the modified method, but the dispersion is practically the same for both. This normal material does not seem to include cases of Gilbert's familial jaundice.

As far as the present author has been able to discover, no comparative study has been made of infected material; in fact, there are on the whole very few investigations into the serum bilirubin in infected conditions. Such have been made by Douglas and Tannenbaum in 1930, and by Cartwright, Wintrobe and co-w. in 1946 (on mixed infected material), the former finding that the values for serum bilirubin in these conditions fell within the limits for the normal, and the latter that they were somewhat lowered.

We consider ourselves justified in presenting the material we have collected, for the following reasons. The values for the normal material have been fairly satisfactorily collected around the mean. In 1937, Pedersen and Waldenström used Svedberg's ultracentrifuge to show that the bilirubin is bound to the serum albumin. There is usually an increase of globulin in infectious conditions. Under such circumstances, it should be reasonable to assume that at any rate not *more* bilirubin is bound in the protein precipitation in the pathological material than in the normal material. In the comparative investigation made by Dirr and Sereslis in 1938 between the original methods and Jendrassik and Cleghorn's modification, there seems to be fairly good agreement between the two procedures, except as regards hepatogenic jaundice, particularly when it is in process of subsiding. The fact that we used an older form of the method should, therefore, not make very much difference.

We now come to the question of how to explain the indubitable falls in the values for serum bilirubin demonstrated in the more active and anaemic cases of rheumatic infection. The

simplest explanation would be that the destruction of the blood is reduced. As we shall be seeing later, there is an increased secretion of urobilin with the urine. Can this be the explanation? Or is there an increased storingup of broken-down haemoglobin inside the organism, as was the case with the iron? No definite answer to these questions can be given at present.

In 1941, Vahlquist was able to show in normal persons a statistically significant correlation between Hb and serum iron on the one hand, and bilirubin and serum iron on the other. In cases of rheumatoid arthritis we have found a significant correlation between Hb and serum iron and, when the material was divided up in certain ways, probable or significant differences between the serum bilirubin values in milder and more severe cases.

There is reason to suppose that the serum bilirubin and serum iron are different links in the same causal chain. When the Hb is broken down, corresponding amounts of iron and bilirubin come into being, and the opposite thing naturally happens when Hb is built up.

When the values for serum bilirubin are lowered in a condition of iron deficiency, it is natural to suppose this is because there is not enough iron at the disposal of the bone marrow, and that the Hb metabolism consequently assumes a lower level. Infectious conditions are unquestionably also attended by a disturbance in the Hb synthesis and the formation of red blood corpuscles, first and foremost as regards quantity. Heilmeyer's school attribute this to a local iron deficiency in the bone marrow, basing this view on the low serum iron and low colour index that often accompany anaemias in infectious conditions. However, there is also a qualitative disturbance in that, as has been mentioned previous, increased quantities of protoporphyrine in the red blood corpuscles and of coproporphyrine III in the urine have been pointed out as indicating a reduction in the Hb synthesis, where in all probability the iron component (Cartwright and co-workers) does not play the main part. In 1946, the present author pointed out the part played by the infections in causing an acute attack in cases of the hereditary disease, not uncommon in Northern Sweden, of porphyria. In

acute attacks of this disease, the Hb and porphyrine synthesis or breakdown stops at a stage where toxic substances belonging to the porphyrines are formed, with a peculiar disease picture in consequence (those interested are referred for further details to Waldenströms monograph on this disease, published 1937). This disease is an extreme special case, but the above observation is important as indicating the interference by infections in the Hb metabolism.

It is reasonable to assume that both the lowered values for serum bilirubin and, indirectly, possibly the serum iron also, are linked up with a hampered and consequently diminished Hb synthesis. It is also possible as regards serum iron that it is a toxic inhibition of the capacity of the iron stores to give off iron to the serum. For further discussion see chapter XI.

The anaemia frequency.

Having now studied the influence of different factors on the composition of the blood, and found that fever, raised S.r., and more pronounced symptoms as a whole, seem to run parallel with the tendency to anaemia, we shall now proceed to get an idea on the anaemia frequency. As stated in the survey of the literature, investigators have not been agreed as to where the boundary-line should be set for what they call anaemia; this is readily understood, since this line is certainly not clear-cut. If, however, a fixed limit is used to get a general idea of the anaemia frequency, the first thing to take into account is that the normal values for red blood corpuscles and Hb are different for men and women. This being so, it is questionable whether the same limit should be used for men as for women. The most natural is to experiment with the normal value diminished with one and two times the standard deviation, as a working hypothesis. This gives 85 % Hb for men and 77 for women, or respectively 79 and 72, if we use the normal figures we have found. These figures might now be suitably rounded off to 85 and 75 for men, and 80 and 70 for women. These limits yield the following figures. See Table 29.

Table 29. *Frequency of anemia in polyarthritic cases from Umeå.*

Limit of Hb, %	Number	in % of 130 ♂ resp. 207 ♀
M e n		
< 75	15	11.5
< 85	54	41.5
75—84	39	30.0
W o m e n		
< 70	47	22.7
< 80	130	62.8
70—79	83	40.1

Thus, this polyarthrititis material shows a considerably higher anaemia frequency in the women than in the men, although the anaemia limit for women has been set lower, thus agreeing with the customary finding that women contract anaemia more often than men.

As we have seen the anaemia frequency is to a greater or lesser extent correlated with factors in the case history or status. For example, we find significant negative correlation between S.r. and the Hb value both for men and for women.

$$\begin{aligned} 130 \text{ men } r \pm \varepsilon(r) &= -0.589 \pm 0.057 \\ 207 \text{ women } r \pm \varepsilon(r) &= -0.312 \pm 0.063 \end{aligned}$$

It would be interesting in this connection to take a closer look at the relation between anaemia and S.r., a relation which has been under discussion in the literature. See below!

The correction of the sedimentation rate in anaemia.

Fåhræus showed in 1921 that the increased sedimentation rate of the red blood corpuscles was mainly due to their intensified aggregation (rouleaux formation), and that the reason for this was to be sought in an increase of the plasma globulins,

the serum globulin and the fibrinogen, the last named, in particular, being of importance here. Basing his statement both on experiments and on theoretical investigation, he said that the relative number of the red blood corpuscles has a certain importance inasmuch as a large number reduces the sedimentation rate and a small number raises it — factors which considerably influence said rate when the composition of the blood shows great deviations from the normal.

Proceeding from the above state of affairs, a number of investigators have set up tables or nomograms for correcting the sedimentation rate in anaemia (Westergren, Gram, Rourke and Ernstene, Wintrobe and Landsberg, Ilynes and Whitby; and others). These tables or nomograms have been drawn up according to the increase in the sedimentation rate obtained by diluting normal blood, usually with the subjects own citrate plasma (oxalate or heparine plasma). The corrected rate is then read off by inserting the clinically observed sedimentation rate against the clinically observed haemoglobin value or red corpuscle count or haematocrite value, sometimes against two of the values given.

Here, the present author will only briefly point out the inaccuracies which result from disregarding the fact that the values for Hb and the red blood corpuscles correspond numerically *only* in normochrome and normocytic states, and those for haematocrite and red blood corpuscles only in normocytic states. In any case, correction of S.r. should be made not for the degree of anaemia but for the degree of oligocythaemia, since it is *the decrease in the number of red blood corpuscles* that causes the rise in S.r. In addition, there is the change in S.r. that can be thought to be due to a micro- or macrocytosis, and possibly also to the fact that, in certain conditions, the red blood corpuscles may be thicker or thinner than normally.

There are objections from purely clinical viewpoints, also. If it is assumed that, as a general rule, an anaemia produces a raised S.r., then all clinically observed anaemias should show a rise of this kind. But they do not. A case of pernicious anaemia may show normal S.r., and so may a case of severe iron-deficiency anaemia. The polyarthritis material presented

here also contains cases with anaemia and normal S.r. There are also a few cases with oligocythaemia and normal S.r.

The above observations justify the statement that, generally speaking at least, anaemia and raised S.r. need not be correlated. Indeed, Lebel and Lottrup (1933) found in clinical material that the uncorrected S.r. fitted the clinical picture better than the one corrected according to Gram, and rejected correction for that reason.

What is the situation in the present author's material? It has been shown earlier on that decreased Hb has a statistically significant correlation with raised S.r. But if the rheumatic infection causes the anaemia, and the anaemia in its turn is mainly responsible for the rise in S.r., conclusions as to the degree of anaemia based on S.r. simply go in a circle. On the other hand, if anaemia and raised S.r. are each caused by the rheumatic infection independently, thus constituting different sides of the latter's harmful action, then the comparison gains in force. One thing showing that the degree of anaemia and raised S.r. do not always run parallel is, of course, that the present author's material contains not a few cases, specially among the men, where the rheumatic infection is accompanied by raised S.r. but normal values for Hb and the red blood corpuscles.

An investigation into the quotients of the fibrinogen and globulin-albumin in polyarthrititis as compared with the S.r. should be of interest in throwing light on these circumstances. Such investigations have been made by Westergren, Theorell and Widström in 1931, and by Svedin and Bengtsson in 1944. Here, the values for the correlation agreed (only the values for the second investigation are given; they concern rheumatic infections). The correlation for S.r. — fibrinogen was 0.82 ± 0.03 , for S.r. — globulin 0.48 ± 0.08 , and for S.r. — albumin — 0.51 ± 0.08 . Olhagen (personal communication from unpublished material) has shown that, in isolated cases where the fibrinogen value is fairly low in raised S.r., the value for the γ -globulin is, on the contrary, high.

In their above-mentioned work, Westergren, Theorell and Widström rejected correction of S.r. for anaemia on the grounds

that the correlation of blood protein (fibrinogen, globulin-albumin quotient) — S.r. was not as strong for the corrected S.r. as for the uncorrected.

The increase in the sedimentation rate of the red blood corpuscles due to a reduction in their number is inhibited by certain known factors. Their diameter is often decreased in polyarthritis (see the chapter on the diameter of the red blood corpuscles). This may be supposed to reduce their size or form, and therewith their sedimentation rate. It is known (Gripvall) that the reticulocytes show a lowered aggregation tendency, and therewith lowered sedimentation rate. Certain cases of polyarthritis show an increased number of reticulocytes, which consequently should also have an inhibiting effect on the sedimentation rate.

It should therefore be warrantable to say that the infectious articular disease and not the anaemia, caused by the infection is the main causal factor in the raised S.r. in polyarthritis. It is impossible to say definitely in the individual case how far the anaemia contributes to this rise. There is reason to repeat emphatically that it is the oligocythaemia, and not the anaemia as such, that has a heightening effect on the sedimentation rate.

CHAPTER VI.

Rheumatoid arthritis, achylia and anaemia.

The earlier literature has been reviewed in Chap. I, and the methods in the chapter on that subject. Chap. I also describes a comparative investigation into the figures for acidity after Ewald's test meal and fractionated test meal with histamine, where it was seen that with a total acidity figure of 8 or less, 50 % of the cases were histamine-negative.

The present author has investigated 80 men and 136 women with Ewald's test meal, for acidity in the stomach. The material has been divided up according to a total acidity of 8 and under and more than 8.

To find whether low figures for the total acidity are more often found combined with anaemia, the table 30 has been made to include values for Hb and red blood corpuscles at different degrees of acidity, and also the acidity in anaemic and non-anaemic cases (cf. table 31).

There are no statistically probable or significant differences either for men or women in any of the tables. The anaemic men may possibly be suspected of a raised anaemia frequency when the total acidity is 8 and under, but the material is too small, and the difference not great. The women show good agreement as regards Hb content in different acidity groups.

If the material is arranged according to type of course before admission (actual progression tendency), as in the table 32, we find a suspicious tendency towards an increase in the number of cases of hypochylia (possibly achylia) in the severer cases,

but no differences are statistically significant, and the severer cases are few.

Table 30. *Distribution of the polyarthritic from Umeå with regard to figures for Hb, RBC and total acidity after test meal.*
 $M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Figures of total acidity	Hemoglobin figures in %			Red blood corpuscles in millions		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
M e n						
8 = I	19	84.53 ± 2.15	9.4	19	4.616 ± 0.092	0.40
9—15 = II	9	92.33	—	9	4.901	—
> 15 = III	52	87.63 ± 1.32	9.5	52	4.729 ± 0.061	0.44
Diff.: I—II		-3.10 ± 2.52			-0.113 ± 0.110	
W o m e n						
8 = I	30	75.03 ± 1.79	9.8	30	4.245 ± 0.069	0.38
9—15 = II	22	75.50 ± 1.95	9.1	22	4.389 ± 0.063	0.30
> 15 = III	84	75.69 ± 1.01	9.2	84	4.229 ± 0.037	0.34
Diff.: $\left\{ \begin{array}{l} \text{I—II} \\ \text{I—III} \\ \text{II—III} \end{array} \right.$	I—II	-0.47 ± 2.65			-0.144 ± 0.093	
	I—III	-0.66 ± 2.06			$+0.016 \pm 0.078$	
	II—III	-0.19 ± 2.20			-0.160 ± 0.073	

Table 31. *Total acidity at admittance in anemic and not anemic cases from Umeå.*

Total acidity	Hb. in %							
	< 74 ♂ = I		75—84 ♂ = II		I + II		> 85 ♂ = III	
	Num- ber	%	Num- ber	%	Num- ber	%	Num- ber	%
M e n								
< 8	4	—	5	20.0 ± 8.0	9	29.0 ± 8.1	10	20.4 ± 5.8
> 8	2	—	20	80.0	22	71.0	39	79.6
Total	6	—	25	100.0	31	100.0	49	100.0
W o m e n								
8	6	20.7 ± 7.5	16	28.6 ± 6.0	22	25.9 ± 4.8	8	15.7 ± 5.1
> 8	23	79.3	40	71.4	63	74.1	43	84.3
Total	29	100.0	56	100.0	85	100.0	51	100.0

Table 32. *Total acidity in arthritic cases from Umeå with different types of course before admittance.*

Total acidity	Type of course before admittance							
	A		B		C		B + C	
	Num-ber	%	Num-ber	%	Num-ber	%	Num-ber	%
M e n								
< 8	9	18.0 ± 5.4	6	24.0 ± 8.5	4	—	10	33.3 ± 8.6
> 8	41	82.0	19	76.0	1	—	20	66.7
Total	50	100.0	25	100.0	5	—	30	100.0
W o m e n								
< 8	10	15.9 ± 4.6	15	24.6 ± 5.5	5	—	20	27.4 ± 5.2
> 8	53	84.1	46	75.4	7	—	53	72.6
Total	63	100.0	61	100.0	12	—	73	100.0

Classifying according to joint status group on admission (degree of activity), we find several cases of achylia in the severer groups, but here, too, there are no statistically probable or significant differences. See Table 33.

Table 33. *Total acidity in arthritic cases from Umeå with different joint status at admittance.*

Total acidity	Joint status at admittance							
	D		E		F		D + E	
	Num-ber	%	Num-ber	%	Num-ber	%	Num-ber	%
M e n								
< 8	7	21.2 ± 7.1	5	16.7 ± 6.8	7	41.2 ± 11.9	12	19.0 ± 4.9
> 8	26	78.8	25	83.3	10	58.8	51	81.0
Total	33	100.0	30	100.0	17	100.0	63	100.0
W o m e n								
< 8	5	17.2 ± 7.0	13	17.8 ± 4.5	12	35.3 ± 8.2	18	17.6 ± 3.8
> 8	24	82.8	60	82.2	22	64.7	84	82.4
Total	29	100.0	73	100.0	34	100.0	102	100.0

An investigation of the total acidity in non-febrile and febrile cases shows that 2 of 4 febrile men showed a figure of 8 or under. However, the small number of febrile men and women make it impossible to conclude anything from this.

Now it is a fact that the frequency of achylia increases with increasing age. But as we have not found any difference in the achylia frequency in the total material, it is unnecessary to go into the age distribution, particularly as the material is too small to allow of closer analysis.

The negative results of the above tabulations should not mislead one into thinking that these figures prove that there is no connection between, say, achylia and anaemia in rheumatic subjects: our inability to obtain figures supporting the existence of such a relation may be due to the fact that the material was too small. Even if it can be said, from a clinical viewpoint, to be large, it is too small from a statistical viewpoint to allow of conclusions. This does not mean that an even larger material could not have yielded differences. In view of the difficulty of procuring large enough materials, the present author has felt justified in publishing the figures obtained: it is not impossible that subsequent investigators may find them useful. It should, however, be pointed out that a possible connection between achylia and anaemia in polyarthritis cannot be so very marked, since if this were so, it would have appeared in our material.

This being so, it will be of interest again to discuss earlier investigations. Readers will remember that the survey of the literature reviewed cases of anaemia and achylia in arthritic subjects. It was found that Edström was the only one with a material worth discussing in this respect. Working with fractionated test meals (with histamine injections when no free HCl was found), he compared the acidity in 432 patients suffering from rheumatoid arthritis with the corresponding conditions in a material of 89 cases suffering from various diseases which could not affect the stomach. Both materials were divided according to age, going up 10 years at a time. If only the age differences are taken into account, we find a difference that is only just significant in the achylia group. However, in groups

divided like this, it is impossible to establish whether the age really is the same. The fact that the mean more or less agree is not conclusive, since this does not rule out the possibility that the various divisions may still be different. This being so, Edström's material cannot be said to lead to fully conclusive results.

CHAPTER VII.

Urobilin values in morning urine in cases of rheumatoid arthritis.

To get something to go on, an investigation was made, on both 20 normal subjects and 20 cases of rheumatoid arthritis of different degrees of severity, as regards the urobilin in the total urine during 24 hours and the morning urine. The methods used have been described in Chap. III. The normal values obtained are given below.

*Morning passed sample and 24-hour quantity of urine
in normal persons:*

<i>Urobilin.</i>	Number of cases	%
0	18	45
1: 4-8 (slight traces)	14	35
1: 8-16 (+)	8	20
Total	40	100

In the morning passed samples the urobilin does not exceed 1: 4-8, and in the 24 hour total it is not over 1: 8-16, regardless of specific gravity. The values are higher as is seen in the table above in the 24-hour quantity; this also holds for the polyarthritis cases. As regards the latter, however, technical reasons forced us to confine ourselves to an investigation of the morning urine. Thus, while the above urobilin values for normal material also include samples from the 24-hour urine and can be taken as maximum morning values, those for the pathological material

consist solely of samples from the morning urine and should probably be regarded as minimum values. The tables below outline the results from the investigation of the arthritis cases.

Table 34. *Urobilin figures in polyarthritic cases from Umeå with different types of course before admittance.*

Urobilin	Type of course before admittance							
	A		B		C		B + C	
	Num- ber	%	Num- ber	%	Num- ber	%	Num- ber	%
M e n								
4—16	22	42.3 ± 6.9	12	40.0 ± 8.9	3	—	15	38.5 ± 7.8
16—32	18	34.6 ± 6.6	13	43.3 ± 9.0	5	—	18	46.1 ± 8.0
32—64	5	9.6 ± 4.1	3	10.0 ± 5.5	0	—	3	7.7 ± 4.3
> 64	7	13.5 ± 4.7	2	6.7 ± 4.6	1	—	3	7.7 ± 4.3
Total	52	100.0	30	100.0	9	—	39	100.0
W o m e n								
4—16	21	36.2 ± 6.3	30	46.1 ± 6.2	5	—	35	44.2 ± 5.6
16—32	20	34.5 ± 6.2	25	38.5 ± 6.0	5	—	30	38.0 ± 5.5
32—64	14	24.1 ± 5.6	8	12.3 ± 4.1	2	—	10	12.7 ± 3.7
> 64	3	5.2 ± 2.9	2	3.1 ± 2.1	2	—	4	5.1 ± 2.5
Total	58	100.0	65	100.0	14	—	79	100.0

Table 35. *Urobilin figures in polyarthritic cases from Umeå with different joint status at admittance.*

Urobilin	Joint status at admittance					
	D		E		F	
	Number	%	Number	%	Number	%
M e n						
4—16	14	48.3	15	38.5	8	34.8
16—32	12	41.4	15	38.5	9	39.1
32—64	2	6.9	6	15.5	—	—
> 64	1	3.4	3	7.7	6	26.1
Total	29	100.0	39	100.0	23	100.0
W o m e n						
4—16	11	50.0	30	40.0	15	37.5
16—32	3	13.6	29	38.7	18	45.0
32—64	6	27.3	12	16.0	6	—
> 64	2	9.1	4	5.3	1	2.5
Total	22	100.0	75	100.0	40	100.0

Table 36. *Urobilin figures in polyarthritic from Umeå with and without fever.*

Urobilin figures	Temperature			
	$\leq 37^{\circ}$		$> 37^{\circ}$	
	Number	%	Number	%
M e n				
4—16	34	41.0	3	—
16—32	34	41.0	2	—
32—64	7	8.4	1	—
> 64	8	9.6	2	—
Total	83	100.0	8	—
W o m e n				
4—16	52	42.9	4	25.0
16—32	40	33.1	10	62.5
32—64	22	18.2	2	12.5
> 64	7	5.8	0	—
Total	121	100.0	16	100.0

Table 37. *Urobilin figures in anemic and not anemic patients from Umeå.*

Uro- bilin	Hb. in %							
	$< 74 \text{ ♂} = \text{I}$		$75 - 84 \text{ ♂} = \text{II}$		I + II		$\geq 85 \text{ ♂} = \text{III}$	
	Num- ber	%	Num- ber	%	Num- ber	%	Num- ber	%
M e n								
4—16	4	—	8	32.0 ± 9.3	12	31.6 ± 7.5	25	47.2 ± 6.9
16—32	6	—	12	48.0 ± 10.0	18	47.4 ± 8.1	18	34.0 ± 6.5
32—64	2	—	2	8.0 ± 5.4	4	10.5 ± 5.0	4	7.5 ± 3.6
> 64	1	—	3	12.0 ± 6.5	4	10.5 ± 5.0	6	11.3 ± 4.3
Total	13	—	25	100.0	38	100.0	53	100.0
W o m e n								
4—16	11	31.4 ± 7.8	25	43.9 ± 6.6	36	39.1 ± 5.1	20	44.4 ± 7.4
16—32	14	40.0 ± 8.3	24	42.1 ± 6.5	38	41.3 ± 5.1	12	26.7 ± 6.6
32—64	8	22.9 ± 7.1	6	10.5 ± 4.1	14	15.2 ± 3.7	10	22.2 ± 6.2
> 64	2	5.7 ± 3.9	2	3.5 ± 2.4	4	4.3 ± 2.1	3	6.7 ± 3.7
Total	35	100.0	57	100.0	92	100.0	45	100.0

91 arthritic men and 137 arthritic women were investigated for the urobilin content in the morning urine. The first thing shown by the above tables is that this content was considerably raised. The difference from the above normal values is quite clear, though this naturally does not prevent a small number from falling within the limits for the normal. Otherwise, no difference is found on comparing groups of different degrees of severity, febrile and non-febrile cases, and anaemic and non-anaemic cases respectively. As has been mentioned before, we should point out that the material is not very large, and that therefore the groups are too small definitively to exclude the possibility of differences in the above respects. A further weakness in the material is that the cases not could be investigated for total urine during 24 hours. No investigation was made to see whether the urobilin secretion in the faeces showed an increase.

It has long been known that a liver lesion raises the urobilin secretion in the urine. There is therefore reason to suppose that such a lesion is present in rheumatoid arthritis. As has already been stated in Chap. I, we do not consider there is sufficient evidence for the contention of Heilmeyer and co-workers that a raised secretion of urobilin in urine and faeces indicates increased destruction of the blood, caused by the disease.

CHAPTER VIII.

The bone marrow, diameter, reticulocytes and epithelial lesions in rheumatoid arthritis.

The bone marrow in infectious and infectious-toxic states.

The anaemia occurring in the above states has, by various authors, often been called aplastic, meaning that it is due to defective function of the bone marrow. This frequently seems to have been taken to mean some atrophic condition, regardless of the fact that investigators as early as Neumann and Bizzozero were able to show that, in states of chronic infection (observed at the autopsy), the bone marrow was hyperplastic. In quite a large number of autopsies, the present author, also has been able to see that persons who have died from infectious diseases had hyperplastic bone marrow in their femoral diaphysis. Its colour was red, or grey and red in patches, and in some cases microscopic check-ups showed this macroscopically hypertrophic marrow to be very rich in cells, indicating that it really did function. It would be interesting to make a systematic study of these matters on autopsy material. The present author's material has not been examined thoroughly enough.

The conclusion one would reasonably draw from these observations is that there is a dysfunction of the bone marrow -- unless, of course, it can be shown that the consumption of the red blood corpuscles outside the bonemarrow in the organism is abnormally high. If it is normal, the production of red blood

corpuscles must in some way be inhibited. It should be interesting to compare bone-marrow punctates from normal persons with the picture of sternal punctates from persons suffering from diseases of an infectious or infectious toxic nature.

Rohr states in 1939 that he investigated a case of septic thrombosis, with achylia. In the peripheral blood he found an Hb value of 44 % and 3.5 million red blood corpuscles. There were 7500 leukocytes. The bone marrow showed 46 erythroblasts to 100 white blood cells; many of the former were immature macroblasts. A renewed investigation 5 weeks later, when the subject was afebrile, showed 78 % Hb and 5.1 million red blood corpuscles in the peripheral blood, while the bone marrow yielded 32 nucleated red blood corpuscles (mainly small, mature normoblasts) to 100 white cells. This was considered to suggest maturity disturbance in the bone marrow. Rohr says that he has seen similar conditions in cystopyelitis, cholangitis, and some other diseases, but he says that in TB, lymphogranuloma, polyarthritis, typhus and ulcerative colitis the erythroblast count was more often normal or below normal.

In 1946 Hemmeler published a material consisting of 25 cases of different acute infections, on which he made 32 sternal punctures. In these cases he was able to pick out an aplastic phase, with immature erythroblasts predominating, and a regenerative phase, with mature erythroblasts predominating. The former is found while the infection is in progress, the latter during recovery. Thus, his investigations bear out Rohr's above-mentioned findings.

Normal material.

The following normal values are on record for the nucleated red blood corpuscles. Only those authors are given who submitted variation limits for their material (cit. Rohr). The figures give the percentage of the total number of nucleated cells. When no differentiation has been made, the cited values constitute the sum of proerythroblasts, macroblasts, and normoblasts.

Arinkin	1929	6.5—18.9	proerythroblasts	0.8—2.9
			macroblasts	} 5.9—16
			normoblasts	
Nordenson	1935	3.6—40.4	proerythroblasts	0 —6
			macroblasts	1 —16
			normoblasts	26 —184
Segerdahl	1935	♂ 12.88 ± 0.61	σ 1.39	
		♀ 11.50 ± 0.51	σ = 3.22	
Young and Osgood	1935	5.4—20		
Weil and Perlés	1936	16—21	proerythroblasts	1.0
			macroblasts	} 15 —20
			normoblasts	
Revol	1938	10.5—39.5	proerythroblasts	10 —38
			macroblasts	} 0.5—1.5
			normoblasts	

This differentiation of the red-cell elements of the bone marrow was done according to Naegeli. Latterly, these cells have instead been differentiated into basophilic, polychromatophilic and oxyphilic erythroblasts. We have used both methods.

In 1940 Rohr investigated 10 normals persons and found the following figures:

total erythroblasts:	13.4—43
basophils:	0.8—10.4
polychromatophils:	2.4—18.8
oxyphils:	6.2—28.6

These figures refer to the number of erythroblasts per 100 white cells. The means were 30 for the total number of erythroblasts, 5 for the basophils, 9 for the polychromatophils, and 16 for the oxyphils, all per 100 white cells.

2) Pathological material.

This material consists of 12 female cases with rheumatoid arthritis. Sternal puncture was made during the days immediately following admission to hospital. Only one puncture was made on each patient. We counted the number of erythrocytes per 500 white cells, and have given the number per 100 white cells.

The material is tabulated below. The first column gives the registration number of the case, the second the age, the third the type of course before admission, and the fourth the joint status group. Then come data as to S.r., Hb value, number of red blood corpuscles, and colour index. For the erythroblast

counts, two groups of values are given: the first for the values per 100 white cells for proerythroblasts, macroblasts, and normoblasts, the second for basophil, polychromatophil and oxyphil erythroblasts. Then come data as to the diameter of the red blood corpuscles, and serum iron.

Reg. no.	Age in years	Course before adm.	Joint status	S. r.	Hb	RBC.	Colour index	Erythroblasts		Diam.	Serum iron
255/42	25	C	F	124	60	3.93	0.75	0—1	6	7.52	78
								5	8		
								17	12		
272/42	45	C	F	85	58	4.43	0.65	0—1	20	7.45	54
								13	12		
								26	6		
265/42	51	B	E	71	85	4.43	0.96	0—1	4	7.94	144
								3	6		
								13	12		
270/42	52	C	F	52	56	4.84	0.58	0—1	8	7.61	48
								10	13		
								21	18		
281/42	27	B	E	32	56	3.88	0.72	1—2	20	7.46	45
								8	12		
								26	12		
295/42	17	B	F	31	73	4.33	0.84	1—2	11	7.61	70
								10	10		
								22	10		
251/42	30	B	E	29	75	4.47	0.88	0—1	10	7.85	80
								5	6		
								18	9		
266/42	51	B	E	21	81	4.39	0.91	0—1	3	7.68	95
								2	8		
								12	8		
308/42	46	B	E	16	75	4.12	0.91	0—1	1		
								5	7		
								26	20		
253/42	56	A	E	15	90	4.67	0.96	0—1	2	7.77	153
								4	5		
								12	10		
268/42	47	A	E	10	51	4.19	0.61	1—2	12	7.55	86
								3	8		
								15	12		
254/42	36	B	E	6	55	4.02	0.74	1—2	12	7.33	45
								8	9		
								10	7		

The numbers for erythroblasts and proerythroblasts have been rounded off upwards or downwards. More exact figures would give a false idea of the exactness of the values. It is generally known that great sources of error attach both to the method of investigation itself and to the differentiation of the cells. The proerythroblast is difficult to distinguish from the myeloblast, and the dividing-line set between macroblast and erythroblast cannot but be subjective: the same thing applies to that between the polychromatophilic erythroblast and the basophilic and oxyphilic ones. But even when these sources of error are taken into account, it is plain that, in certain of the above cases, the erythroblasts show a basophilia which exceeds the limits of the normal. This suggests that, in certain cases, there is an immaturity of the erythroblasts to a degree warranting the diagnosis of a maturity disturbance in the bone marrow as regards the red corpuscle picture.

The small material does not allow of a closer analysis. The essentials in the results, however, seems to agree with the observations made by Rohr and Hemmeler, and this bears out the view which has latterly been taking more and more of a front place — namely, that anaemias in cases of infectious diseases are produced by inhibition of the functions of the haemopoietic organs.

Diameter of the red blood corpuscles in rheumatoid arthritis.

Leaving out of account Bock's erythrocytometry, three ways have come into use for measuring the diameter of the red blood corpuscles, namely 1) in a wet preparation with an ocular micrometer; 2) in a dry preparation with an ocular micrometer, with or without immersion; 3) in a dry preparation with drawing of micro-projection or photography. It is quite clear that the measurement of the red corpuscles' diameter in their own serum will give the smallest artificial changes in their shape and size, since this process obviates both smearing, drying, fixing, and staining. Although a source of error is introduced

when drawing the corpuscles during microprojection, this method has been considered better than measurement with the ocular micrometer (Price-Jones, Mogensen, and others), as it gives smaller subjective errors. Photographing the red blood corpuscles in smear preparations introduces a further source of error; the spherical aberration is probably a special pitfall.

The older literature on the subject has been dealt with by Jørgensen and Warburg in 1927, and Price-Jones in 1933, to mention only a few names. The values for the diameter of the normal red corpuscle, measured according to different methods, were tabulated by Mogensen in 1938. Here, the above-mentioned group 1) contains 6 investigators, with a total of 97 investigated normal subjects. 50-200 cells have been measured, the different investigators' means varying between 7.49 and 8.20^{*} μ . The mean of the means was 7.76 μ . For group 2), the corresponding figures were 13 investigators, 241 normal subjects, 100-1000 cells, from 7.20-8.15 μ , and 7.73 μ , and for group 3) 10 investigators, 469 normal subjects, 200-500 or more cells, from 7.15 to 7.48 μ , and 7.24 μ . To these we can add Hernberg's investigations in 1941 into the age variations in the diameter of the normal red blood corpuscle in normal subjects, carried out according to method 3) above. There was a decrease in the diameter from the neonatal period up to puberty, after which there was a successive increase as the subject grew older, though one only amounting to 0.2 μ from puberty to old age (highest age was 90 years). In the literature, Hernberg is the only one who have found sex-linked difference, and then only in the age group 13-19 years, where the girls showed a rather smaller diameter than the boys.

The present author has not been able to find any published material on the diameter of the red blood corpuscles in cases of infection. There are certain data: Lottrup, for example, in 1929 states in passing that he did not find increased diameter in the red blood corpuscles in investigated cases of joint complaints. Some investigators of renal diseases have found somewhat raised values for the diameter in isolated cases, but in most of them it was normal.

The author's material is set out below. The first column gives the registration number of the case, the second the age, the third the duration of the disease in months (the duration in months since the last exacerbation in brackets), the fourth showing type of course, the fifth showing joint status, the sixth the sedimentation rate; then follow, in turn, haemoglobin, red blood corpuscles, colour index, diameter in μ , acidity of the gastric juice (when Kongo reaction is negative, the figure of the total acidity is given), and serum iron.

M a l e

210/41	38	24	A	E	4	96	5.15	0.93	7.70	+	—	68
200/42	53	42	B	E	12	84	4.52	0.90	7.90	+	—	106
214/42	21	48	A	F	10	78	4.11	0.95	7.49	+	—	135
218/42	42	15	C	F	48	78	4.11	0.95	7.53	—	8	46
223/42	45	4	B	E	7	83	4.40	0.94	7.82	—	0	65
228/42	57	36	B	D	4	81	4.53	0.89	7.69	—	4	185
229/42	55	7	A	D	9	86	4.52	0.95	7.74	—	4	170
242/42	22	2	A	D	3	78	4.36	0.80	7.71	+	—	173
248/42	32	12	B	D	46	81	4.63	0.87	7.72	+	—	101
249/42	40	24	B	E	6	86	4.55	0.94	7.72	+	—	154
256/42	23	60	A	D ?)	3	80	4.23	0.95	7.73	+	—	—
264/42	36	33	A	E	6	86	4.56	0.95	7.77	+	—	145
272/42	31	60	A	F	21	93	4.72	0.99	7.72	+	—	—
280/42	40	36	A	E	9	86	4.72	0.95	7.66	+	—	95
283/42	27	4	A	D	22	76	4.48	0.85	7.70	+	—	—
291/42	38	2	A	D	5	81	4.30	0.94	7.82	+	—	—

F e m a l e

225/41	48	144	A	E	21	68	4.15	0.82	7.65	—	—	28
231/41	21	13	A	E	15	84	4.58	0.92	7.83	—	15	108
272/42	45	36(3)	C	F	85	58	4.43	0.65	7.45	—	4	54
184/42	20	8	A	D	22	86	4.47	0.95	7.65	—	—	—
186/42	42	36(6)	B	E	41	75	4.51	0.75	7.89	+	—	106
211/42	29	67	A	D	6	63	3.77	0.84	7.83	—	—	55
212/42	26	6	B	E	28	64	4.0	0.80	7.72	—	13	80
213/42	51	12	B	E	41	76	4.06	0.95	7.58	+	—	55
208/42	29	40	B	F	65	59	3.60	0.82	7.69	+	—	55
202/42	19	50	B	E	72	73	4.08	0.85	7.68	+	—	81
220/42	48	12	B	E	74	61	3.94	0.77	7.70	+	—	80
222/42	28	48	C	D	16	71	4.02	0.88	7.77	+	—	—
226/42	50	36(5)	A	E	28	61	3.84	0.79	7.89	+	—	65
227/42	22	5	A	E	8	76	4.52	0.84	7.65	+	—	118
230/42	32	18	C	E	8	80	4.50	0.89	7.81	+	—	117
238/42	53	120	B	E	21	75	4.13	0.90	7.69	—	—	—

233/42	44	108(9)	B	E	9	76	4.26	0.89	7.63	—	6	85
251/42	30	24(12)	B	E	29	75	4.47	0.88	7.85	—	—	80
253/42	55	7	A	E	14	90	4.66	0.96	7.77	+	—	152
254/42	38	42	B	E	9	55	4.02	0.74	7.33	+	—	45
255/42	25	29(4)	C	F	124	60	3.93	0.73	7.52	+	—	77
263/42	38	35(10)	B	E	9	80	4.27	0.94	7.76	—	3	58
265/42	51	11	B	E	71	85	4.43	0.96	7.94	+	—	144
266/42	51	7	B	E	21	80	4.39	0.91	7.68	—	7	48
268/42	47	96(22)	A	E	10	51	4.19	0.61	7.55	+	—	86
270/42	29	72(6)	C	F	52	56	4.84	0.58	7.61	—	0	—
277/42	40	120(2)	B	E	22	75	4.29	0.87	7.69	+	—	—
281/42	27	36	B	E	58	56	3.88	0.72	7.46	—	6	45
290/42	18	18	C	F	32	63	4.04	0.78	7.65	—	—	69
293/42	57	11	B	E	53	66	4.24	0.78	7.65	—	15	32
295/42	17	66(4)	B	F	31	73	4.33	0.84	7.61	+	—	70
47/42	41	17	B	E	16	68	3.89	0.89	7.64	—	—	28
184/42	22	8	A	E	34	78	4.41	0.90	7.65	+	—	86

Thus, the material consists of 16 men and 33 women, and is a mixture of mild and severe, anaemic and non-anaemic cases.

$M \pm \epsilon(M)$ is, for the male material, 7.719 ± 0.026 , and for the female 7.661 ± 0.046 . The differences for the total material as compared with the normal material is 0.193 ± 0.029 for men, and 0.251 ± 0.048 for the women, in both cases statistically significant.

The male material is too small for any closer analysis, but a study of the female cases as regards a S.r. value of ≤ 30 and > 30 mm/1h respectively, and an Hb value of ≤ 70 and > 70 respectively, shows no statistically probable or significant differences for the former, but a statistically probable difference for the latter. See table 38.

Table 38. *Red blood corpuscles' diameter in polyarthritic cases from Umeå with different S.r. and in cases with different hemoglobin figures.*

$M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Number	$M \pm \epsilon(M)$	σ	Number	$M \pm \epsilon(M)$	σ	Difference:
S.R. < 30			S.R. > 30 mm/hr.			
19	7.700 ± 0.030	0.132	14	7.645 ± 0.036	0.136	0.055 ± 0.047
Hemoglobin figures $< 70\%$			Hemoglobin figures $> 70\%$			
15	7.617 ± 0.037	0.144	18	7.729 ± 0.025	0.106	-0.113 ± 0.045

Thus, in certain cases of rheumatoid arthritis, especially the anaemic ones, the red blood corpuscles show a reduced diameter when measured with an ocular micrometer in their own serum. However, this may not necessarily mean that the red blood corpuscles in these conditions have a smaller volume than normally. Jörgensen and Warburg (1927) found that the microcytes are thicker than normal red blood corpuscles, though Mogensen (1938) contested this finding.

Enghoff's investigations in 1937 with Bock's method, mentioned in the chapter on the normal material, showed that the diameter of the red corpuscle was smaller in the normal material from Northern Sweden than in similar material from Central and Southern Sweden.

For an idea of the anisocytosis, the present author has studied the dispersion of the diameter measurements in normal and in pathological material. While the rule in the normal material is that the diameter measurement lies between 6.66 and 8.33 μ (3 diameter groups), the dispersion in the pathological material is often greater, comprising 4 diameter groups, and in some cases 5 (in the male material No. 229/42, and in the female Nos 231/42, 254/42, 255/42, 272/42, 281/42 and 293/42). The lowest diameter in the pathological material was 5 μ , and the highest 9.16 μ . Corresponding values in the normal material were 6.66 and 9.16 μ .

Now, we know that the prospects of obtaining a very high or a very low value increases when the material increases in size. Since the normal material is about half as large as the pathological, we may expect the latter to show a greater range of variation if we measure in this way. It is not possible to determine if the increase is to be entirely attributed to this, but it seems not unlikely that the range of variation is greater in the pathological material — a result which, under the circumstances, would be quite natural.

Reticulocytes.

The term 'reticulocyte' is attributed to Krumbhaar (cit. Wintrobe). According to the text-books, the vital granulation was first described by Israel and Pappenheim. It may be mentioned

that the present author, however, has found that it was described before this by Ehrlich in 1892, though this investigator took it to be a degeneration phenomenon. Much has been written about the reticulocytes. Our main concern here will be the normal values and what is known about the reticulocytes in infectious states in adults.

Naegeli, who stained with methylene blue, gave normal values of 1-2 ‰. Older methods using the centrifuge give too high values. Using brilliant cresyl blue, Seyfarth gave a figure of 1-2 ‰. However, in the literature it is found that different investigators get distinctly different normal values from various modifications of these staining methods, so that one is well advised to test out one's own values on normal material. The average for the normal values of more recent date stands between 5 and 10 ‰; this is also borne out by the text-books. A few American investigators submit normal values up to 20 ‰ e.g. Osgood and Wilhelm, (1931). Price Jones and co-workers (1935) submitted normal figures for 81 healthy men, as follows: $M \pm \epsilon(M) = 0.692 \pm 0.047 \%$. $\sigma = 0.425$.

Earlier on, the number of reticulocytes was taken to be the same as that of the polychromatophil red blood corpuscles, but it is now more and more the custom to count the reticulocytes, due to the considerably greater subjectivity in the recording of the polychromatophil cells.

In 1922 Roessingh investigated 4 cases of tuberculosis; he gives no further details. He found normal figures in 3 cases (2-4 ‰) and raised values in 1 case (28 ‰). One case of sepsis beginning to recover yielded Hb 25 % and reticulocytes 120 ‰. This case is interesting, as regeneration had plainly commenced there. In 1912 Luzzatto and Ravenna found somewhat raised figures for reticulocytes in some of 10 cases of different infections with anaemia, i.e. up to 13 ‰, where the normal value was 1-2 ‰. Denecke (1923) found somewhat raised values in 2 cases of tuberculosis and 1 case of puerperal sepsis; on the other hand, there were lowered values in 3 cases of aplastic anaemia following chronically septic diseases. C. Seyfarth states by way of summary in his work of 1927 that,

'as we know, the reticulocytes are materially increased in anaemias, infections, and intoxications'. In 1930, Douglas and Tannenbaum gave an account of 25 infectious states with anaemia, most of them chronic but some of them acute — primarily acute polyarthritis and carditis. Only 1 value was submitted from each case. These cases had normal figures for reticulocytes (authors' normal material 7-13 ‰), except in 1 case of abscess of the lung and 1 of echinococcus of the liver, both of which yielded 20 ‰. None the less they attribute these almost consistently normal figures to the fact that the anaemias were due to defective bone-marrow function. Schilling says briefly in his text book that the number of reticulocytes is raised up to 50 ‰ in anaemizing infections. In 1939 Hubbard and McKee investigated the blood in cases of recurring rheumatic fever with raised sedimentation rate (values not given). They found low values for the reticulocytes, but do not state either the normal values or the method they used. Saifi and Vaughan (1944) found in 10 mild infective cases normal figures for reticulocytes and in 18 infective, septic cases (men and women) high values up to 94 ‰ (normal values up to 20 ‰) for the reticulocytes.

Thus we find that these few examples from the literature yield varying results, which give sporadic glimpses into the reticulocyte metabolism, but actually only momentary ones. Without doubt, the disease states in which the reticulocytes are to be studied need to be followed with repeated determinations over fairly long periods, and the blood should also be studied from other aspects.

Investigations of this kind were made by Cartwright, Wintrobe and co-workers in 1946, and also by Hemmeler in the same year. The former found an increase of the reticulocytes in connection with the restitution of Hb and red blood corpuscles, whereas the latter made the additional finding that, in more chronic cases, a reticulocyte crisis occurred, when the fall in Hb and the red corpuscles ceased, and the blood values assumed a constant, possibly low level, or might even show a tendency to rise.

Normal material (Upsala material).

	Observed figures	
	Highest	lowest
57 ♂ $M \pm \varepsilon(M) = 3.70 \pm 0.30; \sigma = 2.35$	10 ‰	1 ‰
64 ♀ $M \pm \varepsilon(M) = 4.25 \pm 0.32; \sigma = 2.57$	11 ‰	1 ‰

There is no statistically significant or probable sex difference. The material is described in more detail in Chapter IV.

In the Umeå pathological material, reticulocyte investigations were made on 20 men and 32 women, with the following results:

$$\text{♂ } M \pm \varepsilon(M) = 3.35 \pm 0.89; \sigma = 3.97.$$

$$\text{♀ } M \pm \varepsilon(M) = 7.78 \pm 1.05; \sigma = 5.92; D \pm \varepsilon(D) = 3.53 \pm 1.10.$$

Interesting points are the great dispersion in the female pathological material, and the statistically significant difference this material shows from normal material. The same person did not make the counts in the two materials, but the difference should exceed the personal error, which has not been possible to test.

The same material has been classified according to the sedimentation rate as follows: for the men < 10 and ≥ 10 , and for the women < 20 and ≥ 20 mm/1h. The resulting groups of 7 and 10 for the men, and 20 and 12 for the women, show there was no difference between them, so that in this small material the intensity of the disease does not seem to have in any way affected the degree of the reticulocytosis. If the material is divided up according to the duration of the disease, i.e. shorter or longer than 1 year, the new cases of both sexes show a reticulocyte figure 2-3 times higher than that of the old one; this is, of course, not conclusive, since the new cases are so few (6 men and 9 women), but may possibly suggest that the bone marrow in older cases reacts more slowly. We have also followed the reticulocytosis in cases respectively treated and not treated with iron, and submitted the values at admission and discharge to statistical treatment. No statistically significant or probable difference was found between these values, for either sexes. A more detailed discussion of this matter will be found in the chapter on iron treatment.

An observation which the author made clinically was that an ironsensitive anaemia may heal without any noticeable rise in the reticulocyte values during the process. The same observation was made in 1936 by Crosetti and Bajardi in experiments on animals, and on clinical material.

The author has studied cases of rheumatic infections for reticulocytosis and other blood values during longer or shorter periods. There were 34 men and 37 women in the Upsala material, and 13 men and 30 women in the Umeå material. During the period of observation, 9 Upsala women and 17 men on one or more occasions showed reticulocyte values of more than 10 and 8 ‰ respectively. On these occasions, 6 of the women presented rising Hb values, and 3 showed steady Hb; corresponding figures for the men were 9 and 7. Only 1 man with a short period of observation showed a raised reticulocyte count at the same time as a falling Hb value. The highest value observed was 24 ‰. The increase of the reticulocytes seemed to take place immediately before or during the observed rise in the Hb value. Among the female cases, where the reticulocyte values did not exceed the limits given, 9 had rising Hb, 13 steady Hb, and 6 falling Hb, corresponding figures for the men were 8, 6, and 4. Neither the duration of the disease, the type of the course before admission, nor the joint status group could be seen to have any noticeable effect on the reticulocytosis in this small material. Judging from what has been said above, therefore, it seems that a certain increase of the reticulocytes takes place when the Hb values rise, but may also occur under other circumstances.

The same observations may hold for the Umeå material. Of the men, 7 had reticulocyte values > 8 ‰, and of these the Hb values were rising in 4 cases, steady in 1, and falling in 2; 6 men had reticulocyte values of < 8 ‰, the Hb values rising in 3 cases, steady in 1, and falling in 2. Among the women, 16 had reticulocyte values > 10 ‰, with the Hb values rising in 8, steady in 3 and falling in 5; 14 women had reticulocyte values < 10 ‰, with Hb values rising in 5, steady in 8, and falling in 1.

Evidently, then, there is a great deal of variation in these matters, and we might in this context touch on the term 'blood balance'. There is balance when the production and the destruction of the blood correspond to one another. As a rule, it should be warrantable to assume that an increased number of reticulocytes means increased function of the bone marrow. If destruction and production then balance, the values for Hb and red blood corpuscles rise. If, for example, the destructive activity is increased, a raised number of reticulocytes may bring with it static or even falling blood values. A special example of this is the haemolytic anaemia with jaundice. If, on the other hand, the destruction is reduced, a rise in the blood values may occur with normal reticulocyte figures. Then there is the question of the form in which the red blood corpuscles leave the bone marrow. Heilmeyer and Westhäuser (1932) contend that all newly formed red blood corpuscles leaving the bone marrow are reticulocytes. They base their statement on observations in pernicious anaemia and haemolytic jaundice, and also on the relative parallelism which they found between two forms of calculation on blood degeneration respectively on reticulocytosis and excreted urobilin and urobilinogen. Without doubt, their view does not have universal application.

Epithelial lesions in rheumatic infections.

It has long been known that a severe infection, e.g. typhoid fever, could upset the growth of the nails. If the infection did not last long, this disturbance manifested itself as a demarcated, transverse, thin patch, i.e. Beau's lines. Beau's lines might also be due to other causes than infection, e.g. much loss of blood (Bergmark, personal communication). Brittleness in the nails, combined with chlorosis, was described by Marshall Hall (cit. Waldenström) as early as 1833; subsequently, glossy tongue and rhagades at the corners of the mouth, as also Plummer-Vinson's syndrome, have also been attributed to epithelial lesions due to iron deficiency, though doubtless other factors than iron could be shown to play a part. For further

details on this, see Waldenström, 1942. Sjögren's syndrome, keratoconjunctivitis sicca, is also often connected with articular trouble.

There is reason to suppose that it is the thinness and brittleness of the nails which are the primary symptoms of epithelial lesion. The possible koilonychia and splitting of the nails can be assigned to the pressure and wear and tear to which the thin, brittle nails are exposed during work. An example of koilonychia in otherwise probably normal nails are the so-called 'washerwoman nails', where the work in soapy water softens the nails, and pressure causes them to assume a spoon shape. There are, of course, undeniably persons whose nails are constitutionally thin and brittle.

A glossy tongue, or one that has low filiform papillae, is probably a fairly reliable symptom of epithelial lesion. On the other hand, glossy edges to the tongue can, it is thought, have some connection with dentures.

Rhagades in the corners of the mouth have latterly been taken to be mainly a symptom of deficiency.

The present author considered it would be interesting to examine his material for tongue and nail symptoms, as also for the presence of rhagades at the corners of the mouth and trouble in swallowing. Unfortunately this material was not investigated for the occurrence of Sjögren's syndrome. The findings were assessed by the author personally both in the pathological material and in the normal one, which last, innocent of selection, showed no epithelial symptoms (apart from 1 case of thin nails in a woman).

The material and the results of the investigation are tabulated below. The material has been divided up into men and women, and according to the place of residence in country and town. The material was divided up into old and new cases according to the duration of the disease (more, or less, than 2 years).

Rhagades at the corners of the mouth, glossy tongue, and koilonychia are all phenomena which are easily seen; low tongue papillae and glossy edges to the tongue are more difficult, and the former at least is certainly liable to different assessment from different investigators. The same applies to thin nails.

Split nails are a tangible, objective phenomenon, and the patient himself provides information as to their brittleness. The occurrence of flat nails has also been recorded. These studies apply to the nails of the hand. No information was recorded in a certain number of cases, given in the table.

Epithelial symptoms in cases with rheumatic infection.

	Men		Women	
	old cases	new cases	old cases	new cases
<i>Tongue:</i>				
glossy	1	0	2	0
low papillae	2	0	14	6
glossy edges	1	0	6	2
normal	81	28	94	57
unknown	15	2	21	5
Total number of	100	30	137	70
<i>Nails</i>				
koilonychia	0	0	2	2
thin	2	0	6	0
thin and flat	0	0	1	0
thin, split, and brittle	2	2	7	3
brittle	1	0	5	2
brittle and flat	0	0	1	0
brittle and split	2	0	10	5
normal	83	23	86	53
unknown	10	5	19	5
Total number of cases	100	30	137	70
<i>Rhagades</i>	0	0	2	2

No case of Plummer-Vinson's syndrome could be found, and among the men there was no case of mouth rhagades; among the women, 2 new and 2 old cases presented this latter symptom. On the whole, the women showed a considerably greater tendency to epithelial symptoms than the men. Thus, 4 men out of 113 (3.5 %), and 30 women of 181 (16.6 %)

had tongue changes, and 8 men of 110 (7.3 %) and 44 women of 180 (24.4 %) nail changes. As the table shows, the epithelial symptoms are distinctly commoner in old than in new cases, which must be taken as signifying that the duration of the disease plays some part. The intensity of the disease also has some influence here (see below). Contrary to what one would expect, the different kinds of epithelial symptoms are not as a rule all found in one and the same patient.

The 4 men with tongue changes invite a special inspection. In the male material, 1 man showed a glossy tongue and at the same time thin, brittle and split nails. The disease had been going on for 60 months before his admission to hospital, and for 3 months since the last exacerbation. He belonged to the joint status group E.¹ and the type of the course of the disease before admission was A. Hb 93 %, red blood corpuscles 4.81 million, and S.r. 16 mm/1h. No temperature. Free HCl + in the gastric juice. The second case had glossy edges to the tongue (he did not wear a denture) and thin nails. Age 50 years. Type of course: C. Joint status group: F. Duration of disease 15 months: after the last exacerbation 7 months. Hb 81 %. Red blood corpuscles 4.40 million (2 S.r. 27 mm/1h. Serum iron 71 γ %. Gastric juice not investigated. No temperature. The third case had low tongue papillae and brittle nails. Age 43 years. Type of course: A. Joint status group F. Duration of disease 8 years. Hb 80 %, red blood corpuscles 4.9 million. S.r. 18 mm/1h. No temperature. Gastric juice: free HCl 8. Total acidity 16. The fourth case had low tongue papillae but normal nails. Diagnosis: spondylarthritis anchylopoietica. Age 28 years. Type of course: B. Joint status group: F. Duration of disease 2 years. Hb 73 %. Red blood corpuscles 4.03 million. S.r. 26 mm/1h. Serum iron 51 γ %. Gastric juice: free HCl 0. Total acidity 6. No temperature.

3 cases in the male material showed nail changes only. These concerned middle-aged cases of medium polyarthritis. Type of course: 2 were A and 1 was B. Joint status groups: 2 were E and 1 F. Duration of disease 7-72 months. Hb 80-

¹ As for the capitals, used in the following, see chapter IV.

90 %. Red blood corpuscles about 4.5 million. Serum iron $> 100 \gamma$ %. 2 of the cases had free HCl > 20 in the gastric juice, and the case belonging to course type F had a total acidity of 4. No temperature.

These 7 male cases can be regarded as exceptions; only the epithelial changes distinguish them from other, similar polyarthritides cases. It is not clear why just these 7 should have contracted epithelial changes, and it is not stated if any therapy was applied to combat these changes. It is, however, plain that in any case active rheumatic infections are in question.

As already mentioned, the epithelial symptoms were much commoner among the women. 2 new and 2 old cases had mouth rhagades. One of the former cases was a 35-year-old farmer's wife, without objective joint symptoms. Type of course: A. Duration of disease 4 months. Hb 80 %. Red blood corpuscles 4.16 million. S.r. 11 mm/1h. No temperature. Low tongue papillae. Nails normal. The other new case was a 50-year-old farmer's wife. Type of course: B. Joint status group: E. Duration of disease 11 months. Hb 85 %. Red blood corpuscles 4.43 millions. S.r. 71 mm/1h. Serum iron 144γ %. Reticulocytes 9 ‰. Mean diameter of red blood corpuscles 7.94μ . Free HCl in the gastric juice. No temperature. This patient, too, had low tongue papillae, but the nails were normal.

The first of the 2 old cases also had koilonychia and low tongue papillae. Age 42 years. Type of course: C. Joint status group: F. Duration of disease 18 months. Periods of temperature. Hb 64 %. Red blood corpuscles 4.14 million. S.r. 30, some time later 80 mm/1h. She was under observation for a further year and a half, and received long-continued iron therapy per os. A year later, she was showing thin, brittle, and split nails, but no rhagades. Hb 60 %. Red blood corpuscles 4.25 millions. S.r. 50 mm/1h. Serum iron 53γ %. After a further half year, the nails were noted as thin. Still no rhagades. The tongue papillae were low the whole time. Total acidity in the gastric juice was 4. Hb 58 %. Red blood corpuscles 4.43 million. S.r. 85 mm/1h. Serum iron 54γ %. Joint status groups F the whole time.

The second case was a 28-year-old forester's wife. Course type: B. Joint status group: E. Duration of disease 24 months. Hb 75 %. Red blood corpuscles 4.47 million. S.r. 25 mm/1h. Serum iron 80 γ %. Reticulocytes 50 ‰ . Sub-febrile on isolated days. Iron loading: initial value 80, after 2 hours 85, and after 4 hours 78 γ %. Repeated iron loading 40 days later, performed in the same way with $\frac{1}{2}$ gm ferrosi lactas per os, gave the following results: initial value 56, after 2 hours 93, and after 4 hours 100 γ %. Hb was then 76 %, red blood corpuscles 4.46 million, reticulocytes 2 ‰ , and S.r. 38 mm/1h. As well as rhagades at the corners of the mouth, she had low tongue papillae and thin, brittle, split nails.

From the remaining cases, 7 with smooth edges to the tongue fall out, as this symptom cannot be accepted as a definite pathological epithelial one. Only 1 of these 7 cases also showed nail changes.

2 workman's wives aged 37 and 50 years respectively showed glossy tongue, and thin, brittle, split nails. Course type: B and A respectively. Joint status group: E. Both were old cases. Duration of disease was respectively 18 months and 14 years. S.r. 8 mm/1h. Both had free HCl in the gastric juice. No temperature. Hb 81 % and 93 %, and red blood corpuscles 4.30 million and 5.23 million respectively. Serum iron in the second case 153 γ %. These cases are difficult to explain as regards epithelial symptoms and infection, if we may not assume that the symptoms are still living on from an earlier more active phase. — 6 women showed low tongue papillae and brittle split nails, and 1 of them had a clear tendency towards koilonychia. These were 3 new and 3 old cases. Ages 18-51 years. Course type: 5 were B and 1 was C. Joint status group: 1 D, 4 E, and 1 F. Duration of disease 9 months — 10 years. Lowest Hb 61 %, highest Hb 84 %. Lowest red blood corpuscles 3.50 million; highest 4.68 million. Lowest S.r. 8; highest 73 mm/1h. Of 2 subsequently investigated cases, 1 had a total acidity in the gastric juice of 4, and 1 one of 10. A noteworthy factor is the satisfactory rise in the serum iron of 2 cases on iron loading per os in the ordinary way. Case I: Aged 46 years, course type B and joint status group, E. Dura-

tion of disease 9 months. Hb 84 %. Red blood corpuscles 4.45 million. S.r. 8 mm/1h. Total acidity 10. Serum iron with loading as above: 78-200-263 γ %. Case II: Aged 42 years, course type B and joint status group E. Duration of disease 10 years. Hb 76 %. Red blood corpuscles 4.68 million. S.r. 45 mm/1h. Total acidity 4. Serum iron 122-170-286 γ %.

In a further 6 cases, 5 old and one new, there were low tongue papillae but normal nails. In 3 old cases the gastric juice was investigated and the presence of free HCl demonstrated. These 6 cases varied in course type (1 A, 4 B and 1 C) and in joint status group (1 D, 3 E and 2 F). Duration of disease 8 years — 3 months. Lowest Hb 63 %; highest Hb 86 %. Lowest red corpuscles 3.87 m; highest 4.60 m. 4 cases had a S.r. of more than 30 mm/1h, 1 a S.r. of 10 mm/1h, and 1 one of 7 mm/1h.

31 women (10 new and 21 old cases) showed only nail changes; one of these was plainly koilonychia. She was a 34-year-old telephone operator, who had been ill 4 months, and who had only slight articular symptoms. Hb 81 %. Red blood corpuscles 4.36 million. S.r. 5 mm/1h, and serum iron 123 γ %. — For the new cases, the ages varied between 20 and 56 years, the duration of the disease between 3 and 11 months. Type of course: 4 A, 5 B, and 1 C. Joint status group: 4 D, 4 E and 2 F. Hb 61-90 %. Red blood corpuscles 3.71-4.96 million. S.r. 6-125 mm/1h. The gastric juice was examined in 7 cases, and varied from free HCl 42 to total acidity 5. The serum iron in 2 examined cases was 33 and 88 γ % respectively. — In the old cases ages varied between 16 and 54 years, and the duration of the disease between 13 months and 13 years. The duration from the last exacerbation varied from 2-12 months. The type of course showed that mainly active cases were concerned (5 A, 9 B and 6 C): the same applies to the joint status group (3 D, 11 E and 6 F). Lowest Hb 51 %; highest Hb 95 %. Lowest red corpuscles 3.46 m; highest 4.90 m. Lowest S.r. 6 mm/1h; highest 115 mm/1h. The gastric juice was examined in 15 cases, and varied from free HCl 42 to total acidity 8.

Divided up according to the type of the course before admission, the entire female material yields the following

figures: 101 cases from A, 89 from B and 17 from C; of these 12 from A, 26 from B and 10 from C had epithelial changes. Figures for the joint status group for the same material are 56 cases from D, 109 from E and 42 from F, with epithelial changes in 10 cases from D, 26 from E, and 12 from F. Corresponding figures for the male material are 82 cases from A, 39 from B and 9 from C (for course type before admission), with epithelial changes in 4 from A, 2 from B, and 1 from C; for joint status, 49 from D, 52 from E, and 29 from F, with epithelial changes in 2 from D, 1 from E and 4 from F.

In the light of these figures, it is justifiable to say that the more severe cases have epithelial changes more often than the milder ones. The cases where there are no data as to such changes do not upset the proportions between the groups.

The preceding may be *summed up* in the following way. In a rheumatoid arthritis material consisting of 207 women and 130 men, changes in the tongue epithelium were observed in 30 women and 4 men, nail changes in 44 women and 9 men, and rhagades of the corners of the mouth in 4 women. As no such changes (apart from 1 cases of thin nails in a woman) could be shown in a normal material of 68 men and 66 women, not selected as regards epithelial changes, it must be taken as obvious that the rheumatic infection increases the tendency to epithelial symptoms. These symptoms are considerably commoner among women than among men, and there is a percentual predominance of cases where the disease was of rather longer duration; in addition, these symptoms are found more often among severe than among mild cases.

The epithelial symptoms are often but not always combined with one another. Normal values for Hb, red blood corpuscles, S.r., and serum iron do not rule out the occurrence of such changes. In this material glossy tongue was not found together with gastric achylia. Low tongue papillae and nail changes sometimes occurred as sole symptom. Glossy edges to the tongue have no definite significance as a symptom.

CHAPTER IX.

Serum iron.

Normal serum iron and serum iron in infection.

The older view was that iron was to a large extent absorbed in the upper part of the intestine, but was afterwards also secreted in the lower part. Nowadays, the usual belief is that, on the whole, the iron circulates in the body (McCance and Widdowson, Lundholm *et al.*).

When dealing with the iron resources of the organism, it is usual to make a distinction between functional iron, stored iron, and transport iron. The functional iron consists mainly of the iron-containing pigments (e.g. haemoglobin and myoglobin, cytochrome), peroxidases and katalases. The stored iron forms the iron reserves of the body, and is stored in the tissues. The transport iron has been given the name of serum iron, and in the last decade in particular serum iron has been the object of numerous investigations on normal and pathological subjects. We know that in the infectious diseases (with the exception of hepatitis), the value of the serum iron falls fairly far below the normal.

The iron losses of the organism are assumed to be normally very small and easily replaced by resorption of iron from the diet. Conditions of iron deficiency may, however, arise from external (losses of blood) or internal (constitutional or other) causes.

If the serum iron shows low values in a case of anaemia, this is a very plausible phenomenon, since in conditions of iron deficiency at any rate, it is justifiable to assume an iron deficit extending to the whole organism. The situation is different in an infection, where, on becoming infected, a previously healthy person shows low serum iron without losing any iron. And Schaefer (1940) claims to have shown that the organism retains iron in an infection. The regulating mechanism for the serum iron must have changed in some way. See also survey and discussion in chapter XI.

Opinions differ as to the iron and Hb metabolism during infection. Heilmeyer's school seems to think that, during the onset of infection, the cells of the reticulo-endothelial system have an increased need of iron — to complete their catalyst functions, for one thing — and that they therefore absorb and retain the circulating iron. But, based partly on their studies of the urobilin metabolism (see Chapter I) this school also think that an increased degeneration of the blood corpuscles takes place. As pointed out above, it is in point of fact hardly possible at present to say definitely whether the infectious disease states are accompanied by an increased or reduced degeneration of the blood. Many present-day investigators think that the infections are attended by inhibited and reduced haemopoiesis. If this is the sole factor affecting the serum iron, it ought rather to have an enhancing action. And since the serum iron value is lowered, other factors must enter in. This may be the increased need of iron in the reticulo-endothelium, assumed by Heilmeyer. In my opinion, however, there is also the possibility that a regulating mechanism adjusts the height of the serum iron according to the actual requirements of the bone marrow and other iron-consuming organs, leaving the surplus for the organism's iron stores. This theory provides an explanation for the lowering of the serum iron and raising of the iron in store during infectious status which is at least as reasonable as is Heilmeyer's theory.

For the history of the serum iron, see Vahlquist's detailed account (1941).

The method used in my investigations was described by Heilmeyer and Plötner in 1937. The iron to be determined is freed from its protein binding (Vahlquist) by means of 6-normal HCl and the 20 % trichloro-acetic acid used in protein precipitation. A noteworthy point here is that Vannotti and Delachaux (1942) have shown that different amounts of iron are freed from the serum for quantitative determination by acid of different strengths.

The method has been tested out both on known iron solutions and on sera enriched with iron, and been found satisfactory. For purposes of checking up, the Umeå material was submitted to occasional double determinations, yielding slight errors. In the Upsala material, all the values are the means of double determinations.

The following table gives some normal values from healthy subjects from the literature.

Figures for serum iron in healthy persons.

Male = M. Female = F.

Investigator	Year	Sex	Number of cases	Serum iron
Fowweather	1934	M	10	125
		F	10	105
Moore & co-w.	1937	F	15	98
Heilmeyer & Plötner	1937	M	25	126 (81-162)
		F	25	89 (64-128)
Skouge	1939	M	50	118 (79-158)
		F	50	104 (66-164)
Vahlquist	1941	M	50	142 (68-263)
		F	50	123 (53-210)
Hirvonen	1941	M	25	140
		F	25	119
Bröchner, Mortensen & Olsen	1940	M	20	132 (90-194)
		F	20	127 (79-191)
Hemmeler	1946	M	100	132
		F	100	103

Waldenström	1946			
healthy nurses		F	15	113.2 ± 8.2
town population I		F	26	101.4 ± 5.8
» » II		F	54	94.0 ± 3.7
Laurell	1947	M	61	124 (70-214)
		F	39	108 (57-196)

My own normal values were determined from 26 non-intected men of middle age (hospital clientele, mainly suffering from sciatica) and from 21 healthy women (20-30 years of age, hospital staff).

$$\begin{aligned}
 &26 \text{ males. } M \pm \varepsilon(M) = 132.0 \pm 3.9 & \sigma = 17.7 \\
 &21 \text{ females. } M \pm \varepsilon(M) = 103.8 \pm 7.0 & \sigma = 35.9
 \end{aligned}$$

The difference between men and women of 28.2 ± 8.0 is statistically significant. In 1941, Vahlquist discussed in detail the reason of this sex difference, and concluded that hormonal factors are principally responsible.

On normal material he also finds a statistically significant correlation between serum iron and Hb values and between serum iron and serum bilirubin (determined according to Jendrassik and Cleghorn).

It would unquestionably take too long and overburden the present account if we were to give a detailed description of the values obtained by different authors when determining the serum iron in infectious states. The materials are often small, and the information about the cases incomplete. Nor, since the materials are so small, have the relations between serum iron and other blood factors, or any clinical factors, been submitted to statistical treatment.

Determinations of serum iron in infectious diseases have been made by, e.g., Heilmeyer and co-workers (1937 and 1941), Skouge (1939). Büchmann and Heyl (1939), Schaefer (1940), Vahlquist (1941), Hirvonen (1941), Hemmeler (most recently in 1946), Löfgren (1945), Wintrobe and co-workers (1946), Laurell (1947); some investigators using another earlier methods are Thoenes and Aschaffenburg, and Moore and co-workers.

Generally speaking, we can say that all investigators of the serum iron in infectious diseases with the exception of hepatitis

(Warburg and Krebs 1927, Loche and co-workers 1932, Skouge 1939, Hemmeler 1939, Waldenström 1940, Vahlquist 1941), found more or less lowered values.

If we try to draw conclusions from published cases in the light of cases histories and laboratory values, it would seem that there is no hard-and-fast law, connecting the nature or degree (as expressed in S.r. or fever, for example) of the infectious conditions and the serum iron value. However, Heilmeyer and Vahlquist have discussed the possibility of a certain connection between the presence and degree of anaemia in a condition of this kind and the height of the serum iron, and have not found such a connection to be constant. No study has been made on a rather larger material. Heilmeyer and Plötner say they can assess the activity of an infectious process (in the cases they quote, it was tuberculosis) more easily from its serum iron value than on the S.r. Judging from the values quoted, this is the case to a certain extent, but generally speaking it certainly does not apply. This opinion of mine is backed up by Vahlquist and by the values to be seen in the works of Skouge and Hirvonen. A large number of investigators, most recently Cartwright, Wintrobe and co-workers, have shown that the serum iron rises when the patient is getting better. In measles, Schaefer was able to show that the serum iron sank during the incubation period.

One is justified in speaking of a 'forearming' ('Reaktionsbereitschaft') for serum iron. The fall of serum in horses on the injection of diphtheria and tetanus toxins, a fall originally established by Loche and co-workers in 1932, has been retested and found to hold good when other toxins than these are introduced into the organism, as also in haemorrhages and surgical operations of different kinds. On the other hand, no certain change in the serum iron has been found to result from hunger and the administration of food, alcohol or injection of adrenaline or other vegetatively active substances (Heilmeyer and Plötner, Skouge).

The same general remarks as were made above hold for the investigations, made into the behaviour of the serum iron in the

rheumatic infections, which are of immediate interest here, A comparison of diagnosis or data from the case history with the laboratory values from published cases (Heilmeyer and Plötner 1937, Skouge 1939, Büchman and Heil 1939, Hemmeler 1939, Schaefer 1940, Hirvonen 1940, Heilmeyer, Keiderling and Stüwe 1941, Löfgren 1945, Laurell 1947) yields normal or more or less lowered values for serum iron. In all essentials, the rheumatic infections do not seem to differ from other infectious or infectious-toxic states.

Löfgren 1946 who used Barkan and Walker's methods for determining serum iron, assembled a material of normal cases and chronic polyarthritics in the following table:

normal cases	number	mean $\pm$ standard error of the mean
	♂ 17	0.135 $\pm$ 0.0075 mgm %
	♀ 40	0.105 $\pm$ 0.0060
chronic polyarthritis		
	♂ 8	0.042 $\pm$ 0.0070
	♀ 44	0.038 $\pm$ 0.0032

These values for the serum iron in chronic polyarthritis are unusually low. This work does not attempt any calculation of the relation between the serum iron and other blood factors, either. 8 male cases of arthrosis showed 0.100 ± 0.0143 and 7 female cases 0.106 ± 0.0132 .

Serum iron in cases of polyarthritis.

When investigating the normal material and the total pathological Umeå material for serum iron (page 62), we found both a statistically significant sex difference for the normal material and also a statistically significant difference between the normal material and the total material both for men and women.

If the material is divided up according to the type of the course before admission, according to increasing degrees of progression tendency we get for *men*:

Group A.

Nos of cases 44. $M \pm \varepsilon(M) = 107.6 \pm 5.8$ $\sigma = 38.4$

Group B.

$$31. \quad M \pm \varepsilon(M) = 88.8 \pm 7.9 \quad \sigma = 43.8$$

Group C.

$$5. \quad M = 39.6$$

The difference between the groups A and B is 18.8 ± 9.8 , i.e. not statistically probable. As there are so few cases in group C, it will be better for purposes of calculation to make groups B and C into one. For this new group, the number of cases will be 36, and $M \pm \varepsilon(M) = 82.0 \pm 7.4$, $\sigma = 44.6$. The difference between A and B+C is probable, 25.6 ± 9.4 . It is possible that if the number of cases in group C had been larger, significant differences could have been obtained.

If the *female* material is classified according to the type of course before admission we get:

Group A.

$$\text{Nos of cases } 59. \quad M \pm \varepsilon(M) = 83.3 \pm 5.0 \quad \sigma = 38.3$$

Group B.

$$58. \quad M \pm \varepsilon(M) = 70.9 \pm 3.2 \quad \sigma = 24.4$$

Group C.

$$12. \quad M \pm \varepsilon(M) = 50.3 \pm 8.9 \quad \sigma = 30.8$$

The differences, between the groups A and B is 12.4 ± 5.9 , and between B and C 20.6 ± 10.2 are not statistically probable, whereas the difference between A and B+C (15.9 ± 5.9) is. The difference between A and C is statistically significant, i.e. 33.0 ± 10.2 .

As mentioned earlier on, the division of the cases according to the type of course reflects the actual progression tendency of the case, while the division of the cases according to joint status reflects the actual degree of severity of the case. It has been shown above that the type of course before admission, and therewith the progression tendency, affects the height of the serum iron. There is, however, reason to suppose that a division according to joint status on admission (the degree of severity of the case at the time) would give more perceptible differences in the serum iron between the different groups. This is in fact the case.

The joint status groups are denoted D, E and F, according to increasing degrees of severity. See Table 39 next page.

Table 39. Serum iron in γ % in arthritic patients from Umeå in different joint status groups.

$M \pm e(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Joint status	Men			Women			Diff. between different joint status groups		
	Num- ber	$M \pm e(M)$	σ	Num- ber	$M \pm e(M)$	σ	Groups	Men	Women
D	25	110.9 $\pm$ 9.0	44.8	27	87.1 $\pm$ 6.1	31.8	A—B	13.1 $\pm$ 11.0	11.2 $\pm$ 7.3
E	37	97.8 $\pm$ 6.4	39.1	71	75.9 $\pm$ 4.1	34.5	A—C	39.1 $\pm$ 12.9	26.3 $\pm$ 7.9
D+E	62	103.1 $\pm$ 5.2	41.3	98	79.0 $\pm$ 3.4	34.0	(A+B)—C	31.3 $\pm$ 10.7	18.2 $\pm$ 6.0
F	18	71.8 $\pm$ 9.3	39.5	31	60.8 $\pm$ 5.0	27.6	B—C	26.0 $\pm$ 11.3	15.1 $\pm$ 6.5

It is seen, then, that there are statistically significant differences between groups D and F both for men and women, and between D+E and F for women. The latter difference is statistically probable among the men. This can be taken to show that the actual severity of the rheumatic complaint to a large extent determines the height of the serum iron.

Classified according to the morning temperature, we get, for the men:

	$< 37^{\circ} \text{C.}$	
Nos of cases	74.	$M \pm \epsilon (M) = 100.2 \pm 4.3 \quad \sigma = 41.5$
	$> 37^{\circ} \text{C.}$	
Nos of cases	6.	$M = 45.0$

Between these groups, then, there is a considerable difference, but its certainty cannot be calculated due to the small number of febrile cases. If the female material is similarly investigated, we get:

	$< 37^{\circ} \text{C.}$	
Nos of cases	116.	$M \pm \epsilon (M) = 74.4 \pm 3.1 \quad \sigma = 33.6$
	$> 37^{\circ} \text{C.}$	
Nos of cases	13.	$M \pm \epsilon (M) = 74.3 \pm 9.1 \quad \sigma = 32.7$

The difference is 0.4 ± 9.6 . These figures show good agreement, but this may be due to chance, due to the fewness of the febrile cases. As already pointed out, the difference between the male and the female material may be due to the inclusion in the latter of cases with premenstrual rise of temperature.

We have also investigated the behaviour of the serum iron in anaemia of varying degrees, and compared the values obtained from non-anaemic cases. We have drawn up 3 different groups for men: Group I $< 74\%$ Hb, group II $75-84\%$ Hb, and group III $> 85\%$ Hb.

Group I contains 9 cases, with $M = 54.1$, group II 23 cases with $M \pm \epsilon (M) = 99.6 \pm 10.8$ and $\sigma = 51.6$, and group III 48 cases with $M \pm \epsilon (M) = 102.2 \pm 5.4$ and $\sigma = 37.3$. The number of cases in group I was too low for statistical calculation, although in this group has been taken values for serum iron in

cases where a subsequent stay in hospital had revealed an Hb value below the limit given (ordinarily, only the first stay in hospital has been taken into account). All the same, there is clearly a considerable difference. If groups I and II are made into one, the difference from group III is not statistically probable (15.5 ± 10.3).

The *female* material is more illuminating. There, group I contains Hb values $\leq 69\%$, group II values of $70-79\%$, and group III values of $\geq 80\%$. Group I has been eked out as with the men. It then contains 33 cases, $M \pm \epsilon (M) = 56.4 \pm 4.3$, with $\sigma = 24.6$. Group II contains 59 cases, with $M \pm \epsilon (M) = 74.4 \pm 4.2$ and $\sigma = 32.0$. Group III contains 37 cases with $M \pm \epsilon (M) = 91.4 \pm 5.7$ and $\sigma = 34.5$.

The differences between groups III and I (35.0 ± 7.1) and II and I (18.0 ± 6.0) are statistically significant, as is also the difference between group III and the combined groups I and II (23.5 ± 6.5). On the other hand, the difference between III and II (17.0 ± 7.1) is not even statistically probable.

Thus, on female material it has been possible to show statistically that the lower the Hb values, the lower the serum iron. That this could not be demonstrated on the male material is due partly to the small number of cases in the lowest group, and partly no doubt to the fact that, in the men, the serum iron did not seem to fall to the same extent as in the women.

It would now seem most reasonable to suppose that the reason why cases with more serious anaemia have lower serum iron than the milder cases has to do with the infectious process, which in its turn causes the anaemia. To study this more closely, it will be interesting to see if there is any connection between the sedimentation rate and the serum iron. If we calculate this connection, we find a statistically significant correlation both for men and for women. r = correlation coefficient.

Nos of cases of men: 79. $r \pm \epsilon (r) = -0.44 \pm 0.090$

Nos of cases of women: 129. $r \pm \epsilon (r) = -0.26 \pm 0.082$

CHAPTER X.

Iron loadings.

The capacity of the organism to absorb and retain iron in the serum has been studied both in normal persons and also in different diseased subjects. In so doing it is necessary to differentiate between different types of loading, i.e. *per os*, by intramuscular injection, and by intravenous injection.

Peroral iron loading in normal persons according to the literature.

The first to study such loadings *per os* were Moore and co-workers. The serum iron usually rose rapidly and reached its maximum after 2-6 hours; it might get to values of 300-400 γ %, afterwards falling more or less slowly to rather less than the initial figure. Such loading was subsequently carried out by several investigators (e.g. Heilmeyer and Plötner, Heilmeyer and Koch, Skouge, Büchmann, Waldenström, Vahlquist, Cartwright and co-workers), the results tallying approximately with one another, even when different iron preparations and methods of determination were used.

A representative investigation of this kind is that made by Vahlquist (1944) on 23 healthy women. The amount of iron used was $\frac{1}{2}$ gm iron lactate (97 mgm bivalent iron)

	initial value	increase after 2 hrs
M $\pm$ ϵ (M)	116.3 $\pm$ 8.8	+ 90.5 $\pm$ 11.7
σ	42.1	56.2
increase after 4 hrs	6 hrs	8 hrs
+ 90.5 $\pm$ 13.6	63.9 $\pm$ 11.2	+ 27.9 $\pm$ 11.4
65.1	53.8	54.6

Peroral iron loading in normal subjects.

The material consists of 15 healthy men aged 20-40 years, with normal S.r. (5 mm/1h. and lower), and values for Hb and red blood corpuscles within normal limits (Table 40). The individual variation here is considerable, of course, but the fundamental difference from the loading curves yielded by infectious subjects is quite distinct, as can be seen on a comparison with the different curves for the polyarthritis materials. If the loading results in the normal men and the figures for normal women obtained from Vahlquist are compared, it is seen that the rise in serum iron after 2 hours is greater among the latter, suggesting that the resorption of iron takes place more quickly in women than in men.

Table 40. *Different figures of serum iron in healthy men from Umeå after iron loading test.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation
 $D \pm \varepsilon(D)$ = Mean of the differences between the figures before and after iron loading $\pm$ standard error of the mean.

Number	Preliminary fig.		2 hours after iron loading			4 hours after iron loading		
	$M \pm \varepsilon(M)$	$\sigma(M)$	Mean	$D \pm \varepsilon(D)$	$\sigma(D)$	Mean	$D \pm \varepsilon(D)$	$\sigma(D)$
15	123.9 $\pm$ 8.1	31.3	180.9	+56.9 $\pm$ 8.4	32.5	223.5	+99.5 $\pm$ 18.0	69.8

It is plain that, in peroral loading, the resorption from the gastrointestinal canal is of material importance, and investigations have been made to find out just what happens. The acidity of the stomach does not seem to affect the resorption process unduly, at any rate not if the loading is done with water-soluble iron salts (Waldenström, 1944, on material consisting of cases of essential hypochromic anaemia). It can generally be said that it is wise to use salts of this kind, since it would seem from the literature that resorption and consequent rise in serum iron after reduced iron and, in cases of achylia, ferri salts, are in certain cases less swift or less constant (Moore and co-workers, Heilmeyer and Plötner, Skouge). However, their materials were small and, knowing the great

range of variation in examinations of the same persons on different occasions (Waldenström, Vahlquist, and others), these data cannot be said to be certain.

The intramuscular loadings, which are perhaps best suited for throwing light on the state of affairs in cases where there is reason to think that the resorption of iron from the intestine has been reduced, were first given by Waldenström. My own material is unfortunately too small to be representative, and will therefore not be treated in any detail.

Iron loading by intravenous injection in normal subjects according to the literature.

The difficulty has been to obtain a suitable preparation for intravenous injection. Iron ascorbate has been used by Heilmeyer and co-workers (1937) and by Cartwright and co-workers (1946). Like Moore and co-workers, and Waldenström, the present author has used iron and ammonium citrate, kindly supplied by A.B. Pharmacia, Stockholm. The complications sometimes resulting from the injections have been described by Waldenström and Dahl, and my experiences agree with theirs.

Moore and co-workers (1939) injected 1 mgm iron per kg bodyweight into dogs in the form of iron and ammonium sulphate and iron chloride, and obtained a rise in the serum iron from 100-200 to 1500 γ % in 5 minutes, with successive falling of the values down to the initial value in 24 hours. Injection of colloidal iron hydroxide gave only a slight rise of the serum iron value, and this was taken to mean that this substance was treated as a foreign body and was immediately absorbed by the reticulo-endothelium. The cited value of 1500 γ % is very high, and may be due to their method of determination. Otherwise the result is the 'braking' mechanism described by Waldenström (1944), and explained more fully by Laurell (1947). Intravenous loading on normal subjects has been carried out by several investigators, but on very small materials. The values they found agree with one another, however. For such values, see Moore and co-workers, Heilmeyer and Plötner, Heilmeyer and Koch, Skouge.

Waldenström (1944) has a normal material for intravenous iron loading of 18 healthy persons. The initial mean value is $114 \pm 10 \gamma \%$; the mean after five minutes is $291 \pm 10 \gamma \%$, after 1 hour $271 \gamma \%$, and after 2 hours $284 \gamma \%$. Cartwright and co-w. 1946 have followed 5 of 6 investigated cases for 9 hours, after which time the serum iron values had, on the whole, returned to the initial figures. The passage from the blood stream seems in these cases to be relatively slow, probably because the organism was in no immediate need of iron. The position (studied primarily by Waldenström, 1944) is different in the iron-deficiency anaemias, where the iron leaves the blood stream fairly soon after the intravenous injection; the same thing happens, as we shall see, in the infectious states.

Peroral iron loading in persons with infections according to the literature.

1939 Skouge, who worked with peroral iron loadings, only carried out one such loading in a clear case of infection, i.e. a case of exudative lung TB, with S.r. 80 mm/1h. 84 mgm bivalent iron was administered; the serum iron values were $44 \gamma \%$ before this, and 91 and $117 \gamma \%$ 2 and 4 hours respectively afterwards.

In 1942 Bröchner-Mortensen and Stein investigated 12 patients with lung TB by means of iron loading, using 1 gm iron lactate *per os*. In 10 of the patients there was a rise of $6-77 \gamma \%$, and in 2 a fall of $11-13 \gamma \%$, after 4 hours. The authors said that this did not definitely differ from the findings in normal persons, but this statement can hardly be accepted unconditionally.

Peroral iron loading has also been made by Sticotti (1942) on 10 tuberculous men, with 1 gm reduced iron. Only in 3 cases did he obtain rises within the limits for the normal (Cf. Monasterio's and Scotti's values for this: $60-370 \gamma \%$). All case showed free HCl after fractionated test meal. The author attributed the inadequate rise to inadequate iron resorption from the intestine.

In 1946, Cartwright and co-workers gave 7 patients with chronic infections 1 gm iron sulphate *per os*, and after 1-7

hours found little change in the serum iron curve ('the plasma iron level essentially unchanged'). Hemmeler found a similar state of affairs in 10 infectious cases in 1946.

Peroral iron loading tests on polyarthritics.

A total of 38 men and 58 women were loaded in the morning on empty stomachs with $\frac{1}{2}$ gm iron lactate. Samples were taken before loading, and 2 and 4 hours respectively afterwards, and analysed in the usual way. The value of the serum iron in the preliminary sample is included in the material, which has been dealt with in the chapter on serum iron.

We begin with a table of the total material of cases of rheumatoid arthritis loaded with iron. See Table 41.

Table 41. *Different figures of serum iron in polyarthritic cases from Umeå in iron loading test.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation.

$D \pm \varepsilon(D)$ = Mean of the differences between the figures before and after iron loading $\pm$ standard error of the mean.

Number	Preliminary figure		2 hours after iron loading			4 hours after iron loading		
	$M \pm \varepsilon(M)$	σ	Mean	$D \pm \varepsilon(D)$	$\sigma(D)$	Mean	$D \pm \varepsilon(D)$	$\sigma(D)$
M e n								
38	113.6 ± 7.1	43.6	147.5	33.9 ± 5.6	34.6	141.3	27.7 ± 6.3	38.7
W o m e n								
58	84.5 ± 4.2	31.9	128.6	44.1 ± 5.7	43.3	144.4	59.8 ± 9.0	68.6

The table shows that the initial values for the serum iron before loading were, both for men and for women, lower than in the normal material, and that the figures for the rise of serum iron in the total material -- which includes both mild and severe cases -- is lower than in the normal material. Table 42 gives the differences between the normal figures and the figures for polyarthritics (normal figures for men, see table 40; as normal figures for women Vahlquist's figures on p. 126 have been used).

Table 42. *Comparison between the effects of iron loading in normal cases and in polyarthritic cases. (Cf. Table 40.)*

	M e n	W o m e n
	Differences between normal cases and polyarthritic cases	
Before the test	10.3 ± 10.8	31.8 ± 9.8
2 hours after	23.0 ± 10.1	46.4 ± 13.0
4 " "	71.8 ± 19.1	30.7 ± 16.3
	Differences between normal cases and polyarthritic cases in joint status E + F	
Before the test	19.2 ± 12.2	35.3 ± 10.1
2 hours after	33.0 ± 10.4	55.0 ± 13.3
4 " "	81.0 ± 19.9	46.7 ± 16.3

For the *men*, there is a statistically significant difference between the 4-hour values, and, if a comparison is made with the severer cases (joint status group E + F), for the 2-hour values also, although there was no statistically significant or probable difference for the values before loading. For the *women*, there are statistically significant differences between the normal and the pathological material for all values except that found after 4 hours. But this difference becomes statistically probable if a comparison is made with the severer cases of rheumatoid arthritis (joint status group E + F).

For a closer study of the factors influencing the iron loadings, the material has been divided up according to the type of the course before admission, the joint status group on admission, S.r., whether the subject was febrile or non-febrile, and whether anaemia was or was not present.

As regards type of course before admission, the material has been divided into the usual groups A, B, and C. The male and female material yield no statistically probable or significant differences for the preliminary sample with regard to the mean values for serum iron. In spite of this, the women — though not the men — show statistically significant differences between

A and B and A and B+C (the two latter made into one to make the material larger) for serum iron values taken 2 hours after loading; values taken 4 hours after loading show statistically probable differences. See Table 43.

If the material is divided up according to joint status on admission, the differences become still plainer, Table 44.

Table 43. *Serum iron in iron loading tests in polyarthritic cases from Umeå with different types of course before admittance.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation.
 $D \pm \varepsilon(D)$ = Mean of the differences before and after iron loading $\pm$ standard error of the mean; σ = standard deviation.

Type of course before ad- mittance	Number	Preliminary fig.		2 hours after iron loading			4 hours after iron loading		
		M $\pm$ ε (M)	σ	Mean	D $\pm$ ε (D)	σ (D)	Mean	D $\pm$ ε (D)	σ (D)
M e n									
A	25	119.2 $\pm$ 7.9	39.3	153.0	33.8 $\pm$ 6.2	31.2	148.1	28.9 $\pm$ 7.8	38.8
B	11	114.9 $\pm$ 13.6	45.0	149.0	34.1 $\pm$ 13.4	44.5	143.8	28.9 $\pm$ 12.8	42.4
C	2	36.0	—	69.5	33.5	—	42.5	6.5	—
B + C	13	102.8 $\pm$ 14.1	50.8	136.8	34.0 $\pm$ 11.6	41.7	128.2	25.4 $\pm$ 11.1	40.0
Diff.: A—B		4.3 $\pm$ 15.7			0.3 $\pm$ 14.8			0 $\pm$ 15.0	
» A—(B + C)		16.4 $\pm$ 16.2			0.2 $\pm$ 13.2			— 3.5 $\pm$ 13.6	
W o m e n									
A	20	97.8 $\pm$ 8.7	38.9	164.0	66.2 $\pm$ 8.2	36.6	193.7	95.9 $\pm$ 16.0	71.4
B	33	77.7 $\pm$ 4.6	26.4	110.2	32.5 $\pm$ 7.5	42.9	118.8	41.1 $\pm$ 10.7	61.4
C	5	76.8	—	108.5	31.6	—	116.2	39.4	—
B + C	38	77.6 $\pm$ 4.2	25.9	110.0	32.4 $\pm$ 7.0	43.0	118.4	40.8 $\pm$ 9.9	60.8
Diff.: A—B		20.1 $\pm$ 9.8			33.7 $\pm$ 11.1			54.8 $\pm$ 19.2	
» A—(B + C)		20.2 $\pm$ 9.7			33.8 $\pm$ 10.8			55.1 $\pm$ 18.8	

There are now statistically significant differences in the *female* material between groups D and E and D and F not only in the values after both 2 and 4 hours, but also in D and F as regards the preliminary sample, which yields a probable difference between groups E and F. In addition, the *male* material now shows statistically probable differences between group D and

group E + F for the serum iron values taken 2 and 4 hours respectively after loading.

It is difficult to assess the iron-loading situation in febrile and non-febrile cases, due to the fewness of the former. Therefore those figures are not published.

Table 44. *Serum iron in iron loading tests in polyarthritic cases from Umeå with different joint status at admittance.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean;

$D \pm \varepsilon(D)$ = Mean of the differences between the figures before and after iron loading $\pm$ standard error of the mean; σ = standard deviation.

Joint status at admittance	Number	Preliminary test		2 hours after iron loading			4 hours after iron loading			
		$M \pm \varepsilon (M)$	σ	Mean	$D \pm \varepsilon (D)$	$\sigma(D)$	Mean	$D \pm \varepsilon (D)$	$\sigma(D)$	
M e n										
D	13	130.6 ± 9.9	35.7	183.7	53.1 ± 9.7	35.0	176.0	45.4 ± 6.3	22.7	
E	17	116.9 ± 10.2	41.9	145.4	28.5 ± 8.0	33.0	132.8	15.9 ± 11.5	47.4	
F	8	78.6	—	93.0	14.4	—	103.0	24.4	—	
E + F	25	104.7 ± 9.1	45.3	128.6	23.9 ± 6.1	30.5	123.2	18.5 ± 8.5	42.3	
Diff.: D—E		13.7 ± 14.3			24.6 ± 12.6			29.5 ± 13.1		
» D—(E + F)		25.9 ± 13.4			29.2 ± 11.5			26.9 ± 10.6		
W o m e n										
D	12	98.3 ± 6.1	21.2	175.3	77.0 ± 8.2	28.6	219.8	121.5 ± 19.7	68.1	
E	36	86.1 ± 5.8	35.0	126.9	40.8 ± 7.6	45.6	135.5	49.4 ± 10.8	65.1	
F	10	62.3 ± 6.4	20.4	78.7	16.4 ± 8.2	26.0	85.9	23.6 ± 11.2	35.5	
Diff.: D—E		12.2 ± 8.4			36.2 ± 11.2			72.1 ± 22.5		
» D—F		36.0 ± 8.8			60.6 ± 11.6			97.9 ± 22.7		
» E—F		23.8 ± 8.6			24.4 ± 11.2			25.8 ± 15.6		

When the material is divided up according to a S.r. of respectively 10 or less and more than 10 mm/1h for the men, and 20 or less and more than 20 mm/1h for the women, we find a difference between the preliminary samples, though it is neither statistically probably nor significant. See Table 45.

Table 45. *Mean figures of serum iron before, respectively 2 and 4 hours after iron loading in polyarthritic men and women from Umeå distributed with regard to sedimentation rate.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean; σ = standard deviation.

	S.r. ≤ 10 mm/1h in men S.r. ≤ 20 mm/1h in women			S.r. > 10 mm/1h in men S.r. > 20 mm/1h in women			Diff.
	Number	$M \pm \varepsilon(M)$	σ	Number	$M \pm \varepsilon(M)$	σ	
M e n							
Prelim. figure	22	124.7 ± 8.1	38.0	16	98.3 ± 11.8	47.3	26.4 ± 14.3
2 h. after	22	172.5	—	16	113.1	—	—
4 h. after	22	163.6	—	16	110.6	—	—
W o m e n							
Prelim. figure	31	93.2 ± 5.5	30.4	27	74.6 ± 6.1	31.8	18.5 ± 8.2
2 h. after	31	152.0	—	27	101.8	—	—
4 h. after	31	178.0	—	27	105.8	—	—

We can plainly see the reduced rise in serum iron on loading in the cases where the S.r. is higher. This rise can be studied statistically. See Table 46.

Table 46. *The average increase of serum iron after iron loading per os in men and women distributed with regard to sedimentation rate.*

$D \pm \varepsilon(D)$ = Mean of the differences between the figures before and after iron loading $\pm$ standard error of the mean; σ = standard deviation.

	S.r. < 10 mm/1h in men S.r. < 20 mm/1h in women			S.r. > 10 mm/1h in men S.r. > 20 mm/1h in women			Diff.
	Number	$D \pm \varepsilon(D)$	σ	Number	$D \pm \varepsilon(D)$	σ	
M e n							
Prelim. fig.—2 h. after	22	47.8 ± 7.4	34.7	16	14.8 ± 6.1	24.5	33.0 ± 9.6
Prelim. fig.—4 h. after	22	39.0 ± 7.5	35.1	16	12.3 ± 9.8	39.0	26.7 ± 12.3
W o m e n							
Prelim. fig.—2 h. after	31	58.8 ± 7.2	39.9	27	27.1 ± 8.1	42.3	31.7 ± 10.8
Prelim. fig.—4 h. after	13	84.8 ± 12.9	72.0	27	31.1 ± 10.4	54.2	53.7 ± 16.6

There are statistically significant differences for men between the serum iron values 2 hours after loading; the women show such differences both 2 and 4 hours after loading.

A survey of the peroral iron loadings of anaemic and non-anaemic cases in the table 47 shows that there are no statistically significant or probable differences for the men either between the preliminary samples or the values after 2 and 4 hours respectively: this is true whether groups III and II or groups III and I + II are compared. The women, on the other hand, show statistically significant differences between groups III and I and III and I + II for the preliminary sample, and a statistically probable difference for the values after 2 hours between groups III and II.

Table 47. *Serum iron in iron loading tests in anemic and not anemic patients from Umeå.*

$M \pm \varepsilon(M)$ = Mean $\pm$ standard error of the mean;

$D \pm \varepsilon(D)$ = Mean of the differences between the figures before and after iron loading $\pm$ standard error of the mean; σ = standard deviation.

HB.	Number	Prelim. fig.		2 h. after iron loading			4 h. after iron loading		
		M $\pm$ ε (M)	σ	Mean	D $\pm$ ε (D)	σ (D)	Mean	D $\pm$ ε (D)	σ (D)
M e n									
< 74=I	1	65.0	—	69.0	4.0	—	113.0	48.0	—
75—84=II	13	111.3 $\pm$ 14.6	52.7	143.4	32.1 $\pm$ 10.2	36.9	135.0	23.9 $\pm$ 13.3	48.0
I + II	14	108.0 $\pm$ 13.9	52.1	138.1	30.1 $\pm$ 9.7	36.2	133.6	25.6 $\pm$ 12.4	46.6
> 85=III	24	116.8 $\pm$ 7.9	38.9	153.0	36.2 $\pm$ 7.0	34.2	145.8	29.0 $\pm$ 7.0	34.3
Diff.: III—II		5.5 $\pm$ 16.6			—4.1 $\pm$ 12.4			—5.1 $\pm$ 15.0	
„ III—(I + II)		8.8 $\pm$ 16.0			—6.1 $\pm$ 12.0			—3.4 $\pm$ 14.2	
W o m e n									
< 69=I	16	60.4 $\pm$ 5.6	22.5	107.2	46.8 $\pm$ 17.5	70.2	112.7	52.3 $\pm$ 16.9	67.6
70—79=II	19	84.9 $\pm$ 8.3	36.3	110.5	25.6 $\pm$ 6.8	29.5	125.6	40.6 $\pm$ 12.5	54.4
I + II	35	73.7 $\pm$ 5.5	32.8	109.0	35.3 $\pm$ 7.4	43.8	119.6	45.9 $\pm$ 10.2	60.2
> 80=III	23	101.0 $\pm$ 4.9	23.5	158.4	57.4 $\pm$ 8.5	40.9	182.0	81.0 $\pm$ 15.6	74.8
Diff.: III—I		40.6 $\pm$ 7.4			—10.6 $\pm$ 19.5			—28.7 $\pm$ 23.0	
„ III—II		16.1 $\pm$ 9.6			—31.8 $\pm$ 10.9			—40.4 $\pm$ 20.0	
„ II—I		24.5 $\pm$ 10.0			21.2 $\pm$ 18.8			11.7 $\pm$ 21.0	
„ III—(I + II)		27.3 $\pm$ 7.4			—22.1 $\pm$ 11.3			—35.1 $\pm$ 18.6	

Now, what are the implications of these findings? It is plain that the rise in the serum iron after 2 and 4 hours respectively is considerably smaller in certain cases of rheumatoid arthritis than in the normal material, and also smaller in severer than in milder cases. The clearer results in the female material is due to the fact that, among those thus loaded with iron, there are several severe cases of articular disease.

A study of intravenous iron loading (see below) has shown us that what happens is that the iron leaves the blood stream more quickly in infected cases than in, say, normal material. The same thing perhaps applies here. We have not sufficient reason to suppose (but can on the other hand not dismiss the possibility) that the lower values for the rise in serum iron are due to another factor, e.g. lowered or retarded resorption from the gastro-intestinal canal. However, Hahn, Bale and Whipple found 1946 when experimenting on anaemic dogs with turpentine abscess or Bartonella infection, lowered resorption of radioactive iron from the gastro-intestinal canal as compared with anaemic dogs without abscess or infection. For further discussion, see chapter XI.

There are also cases of rheumatoid arthritis dosed with iron where the value for the serum iron after 4 hours was lower than in the same test before loading. The loading seems able to set up iron secretion from the blood stream to the tissues.

The saturation limit described by Laurell in 1947 can hardly have any very important bearing in these cases, since only by way of exception did this limit fall below 200 γ %, even in cases of chronic polyarthritis with high S.r.

Iron loading by intravenous injection in cases with infection according to the literature.

Heilmeyer and Plötner (1937) injected 10 mgm of iron ascorbate into 3 cases of infection and 1 case of tabes during fever due to pyrifur injections; they found that, after 3 minutes, the rise of serum iron was considerable; about 200 γ % in both normal and infected cases. On the other hand, after 40 minutes

the fall from the 3-minute value averaged 28 γ % for normal cases (5 subjects) and 90 γ % for the infected material. Skouge (1939) obtained similar results on isolated cases. Comparing 7 cases of chronic infections with 6 normal cases, Cartwright, Wintrobe and co-workers (1946) found that the values in the former did not rise as high after 5 minutes as those in the latter. After 3-4 hours, however, the values for the infected cases were down to and below the starting value, while those for the normal material did not get as low as this until after 8-9 hours.

These cases loaded by means of intravenous injection are more easily assessed because the resorption factor drops out. It seems that the iron leaves the blood stream more rapidly when an infection is present than under normal circumstances. It would be reasonable to assume an increased secretion of iron to certain organs, and in point of fact it has been possible to show (Greenberg and co-workers, 1947) with the help of radioactive iron that the liver and spleen absorb larger quantities of iron during infections than normally. The experiments were made on dogs and rats. It is probable that, as Heilmeyer said, the iron is localised in the reticulo-endothelium. Gross, Sandberg and Holly also showed in 1942 that, in infections, the liver and spleen contained more iron than normally.

Iron loadings by intravenous injection in cases with polyarthritis.

This material consisted of 16 men and 12 women, belonging to the Upsala material. All had active rheumatic infections, and 6 men and 3 women were recorded as having acute polyarthritis. All are loaded by injection of 10 mgm iron (as iron and ammonium citrate).

Table 48 gives the values for the serum iron for men and women, and for men + women, before the intravenous injection of iron, and 5 minutes, 1 hour, and 2 hours after the injection, and table 49 gives the differences between the initial value of the serum iron and the values obtained later.

Table 48. *Figures of serum iron before and at different times after iron loading by intravenous injection. Uppsala polyarthritic material.*

$M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean, σ = standard deviation.

	Men			Women			Men + Women		
	Num- ber	$M \pm \epsilon(M)$	σ	Num- ber	$M \pm \epsilon(M)$	σ	Num- ber	$M \pm \epsilon M$	σ
Immediately before injection	16	94.8 ± 10.7	42.9	12	53.8 ± 6.9	23.8	28	77.2 ± 7.8	41.0
5 min. after "	16	258.8 ± 12.5	49.9	12	249.7 ± 11.4	39.5	28	254.9 ± 8.5	45.2
1 hour " "	16	228.0 ± 14.5	57.9	12	218.8 ± 14.0	48.4	28	224.0 ± 10.1	53.3
2 hours	16	203.9 ± 17.7	70.9	12	186.0 ± 15.1	52.5	28	196.2 ± 11.9	63.2

Table 49. *Individual differences between figures of serum iron before iron loading by intravenous injection and different times after loading. Uppsala polyarthritic material.*

$D \pm \varepsilon(D)$ = mean of the differences $\pm$ standard error of the mean, $\sigma(D)$ = standard deviation.

	Number	Diff. between figures of serum iron before loading of iron and					
		5 min. after		1 hour after		2 hours after	
		$D \pm \varepsilon(D)$	$\sigma_{(D)}$	$D \pm \varepsilon(D)$	$\sigma_{(D)}$	$D \pm \varepsilon(D)$	$\sigma_{(D)}$
Men	16	163.9 $\pm$ 9.6	38.5	133.2 $\pm$ 8.0	31.9	109.1 $\pm$ 10.1	40.4
Women	12	249.7 $\pm$ 11.3	39.0	165.0 $\pm$ 13.6	47.2	132.3 $\pm$ 12.4	42.9
Men + Women	28	177.6 $\pm$ 7.8	41.3	146.8 $\pm$ 7.9	41.6	119.0 $\pm$ 8.0	42.3

It is plain that there was a considerable rise in the serum iron after 5 minutes, and that it subsequently fell more and more: an examination of the material in respect of the severity of the disease gives the impression that the serum iron falls more rapidly in severer than in milder cases of rheumatic infection.

A comparison between this material and a normal material loaded intravenously with iron would be of interest. And Professor Waldenström has very kindly placed at the disposal of the present author a normal material he has assembled of intravenous iron loadings on 18 subjects, male and female, loaded once or twice by injection in the same way.

Waldenström's normal material of intravenous iron loadings.

(The statistical calculation was carried out by the present author.)

Serum iron.		
Preliminary fig.		
N = 20	$M \pm \varepsilon(M) = 115.5 \pm 9.5$	$\sigma = 42.3 \gamma \%$
After 5 minutes		
N = 20	$M \pm \varepsilon(M) = 290.3 \pm 9.6$	$\sigma = 42.9 \gamma \%$
After 1 hour		
N = 20	$M \pm \varepsilon(M) = 270.5 \pm 10.9$	$\sigma = 48.9 \gamma \%$
After 2 hours		
N = 13	$M \pm \varepsilon(M) = 284.2 \pm 10.5$	$\sigma = 37.9 \gamma \%$

As, therefore, the initial values are far lower in my pathological material than in Waldenström's normal material, it is not surprising that the curves differ even after iron loading. The question now is whether the rise subsides more quickly in my material than in Waldenström's. The figures would seem to suggest this. For the differences, see table 50, which shows the rise of the serum iron from the initial value after different intervals of time.

Table 50. *Individual differences between figures of serum iron before loading by intravenous injection and different times after loading. Comparison between Prof. Waldenström's normal cases and the present author's polyarthritic cases from Uppsala.*

$D \pm \varepsilon(D)$ = mean of the differences $\pm$ standard error of the mean, $\sigma(D)$ = standard deviation.

Difference between figures of serum iron before loading of iron and	Prof. Waldenström's normal material			The present author's polyarthritic material from Uppsala			Diff.
	Num- ber	$D \pm \varepsilon(D)$	$\sigma(D)$	Num- ber	$D \pm \varepsilon(D)$	$\sigma(D)$	
5 min. after	20	174.8 ± 11.2	50.1	28	177.6 ± 7.8	41.3	-2.8 ± 13.6
1 hour after	20	155.0 ± 11.4	51.1	28	146.8 ± 7.9	41.6	8.2 ± 13.9
2 hours after	13	168.1 ± 15.6	56.1	28	119.0 ± 8.0	42.3	49.1 ± 17.5

It is also seen that the difference between the rise obtained after 2 hours in Waldenström's material (i.e. 168.1 ± 15.6) and that obtained in mine (i.e. 119.0 ± 8.0) shows a difference (i.e. 49.1 ± 17.5), exceeding what can, from a statistical viewpoint, be termed probability, though not reaching significance. Thus, it is very likely that the rise in the serum iron after intravenous iron loading subsides more rapidly in a case of infectious anaemia than in normal subjects.

However, as already mentioned, an examination of the material has given me the definite impression that the rise in serum iron subsides more rapidly in the severer pathological cases than in the milder ones. To investigate this, I have drawn

up table 51, where only those pathological cases have been included which had a sedimentation rate higher than 30 mm/hr.

Table 51. *Individual differences between figures of serum iron before loading by intravenous injection and different times after loading. Comparison between Prof. Waldenström's normal cases and the present author's polyarthritic cases from Uppsala in whom S.r. exceeds 30 mm/hour.*

$D \pm \varepsilon(D)$ = mean of the differences $\pm$ standard error of the mean, $\sigma(D)$ = standard deviation.

Difference between figures of serum iron before loading of iron and	Prof. Waldenström's normal material			The present authors po- lyarthritic cases from Uppsala, in whom S. r. exceeds 30 mm/hour			Difference
	Num- ber	$D \pm \varepsilon(D)$	$\sigma(D)$	Num- ber	$D \pm \varepsilon(D)$	$\sigma(D)$	
5 min. after	20	174.8 ± 11.2	50.1	21	170.9 ± 8.6	39.5	3.9 ± 14.1
1 hour after	20	155.0 ± 11.4	51.1	21	137.1 ± 9.0	41.4	17.9 ± 14.5
2 hours after	13	168.1 ± 15.6	56.1	21	105.0 ± 7.7	35.1	63.1 ± 17.4

We now see that the difference between the normal material and this pathological material is statistically significant for serum iron after 2 hours. This fact cannot be attributed to a quicker resorption of iron, since intravenous injections are in question. The rise after 5 minutes also shows good agreement. The disappearance of the iron from the plasma must be due to its absorption into the iron-stores, or to excretion. As mentioned above, the first alternative is the probable one. This happens more quickly in severer cases of infection than in milder ones.

CHAPTER XI.

Course of anaemia, iron loading before and after iron treatment and effect of therapy.

Survey and discussion of iron metabolism from a theoretical point of view.

When assessing the course of the anaemia, the result of iron therapy, and similar questions, it is necessary to have some idea of the iron metabolism and of the effect iron dosage may have. As first maintained by McCance and Widdowson in 1937, and Lundholm in 1939, the old view that iron is resorbed and then secreted in the intestine is certainly wrong. The iron circulates through the body, and only that amount needed to cover possible losses is resorbed. This is how Lundholm explains the fact that hypochromic anaemia is so much commoner in women than in men. Hahn, Whipple and co-workers, and Greenberg and co-workers *et al.* have shown by experiments on animals in 1938 and later that the subjects did not resorb radio-active iron if they had not previously suffered losses of blood. This should finally prove McCance's and Lundholm's theory. For the rest, the body has a very small iron content, normally amounting to about 5 gm. This iron is shared out between haemoglobin, etc, iron-stores in liver and spleen, bone marrow and, finally, the blood plasma.

When anaemia appears in a patient with rheumatoid arthritis, it can be assumed — as already pointed out in this work — that this is not due to iron deficiency. Probably, the production of red blood corpuscles and haemoglobin gets less, and there

is some inhibition in the function of the red bone marrow. However, there might be iron deficiency if iron is lost more than normally. No signs of this have been found, but the problem seems to need further investigation. Schaefer claims to have shown, by means of iron-balance tests, that a retention of iron takes place during infectious states, but it must not be forgotten that such tests are not wholly reliable. If an extremely slight surplus or deficit of iron is present, it would naturally have a very great effect after some time. Even the most painstaking tests for iron balance cannot give that degree of exactness where small daily differences can be considered out of the question. From this viewpoint, iron balance tests are of little interest. On the other hand, we have ascertained increased secretion of urobilin in the urine. This may be because urobilin-forming substances, e.g. haemoglobin, are destroyed more than normally, or because the function of the liver is upset — probably the latter, since the investigations made on a few cases both by other authors and the present author into the resistance of the blood corpuscles to salt solutions have yielded normal conditions. This problem is already discussed in Chapter I p. 21.

As regards the part played by the blood plasma, it should be pointed out that plasma is a means of transport, and that the iron content may therefore be higher if more iron is resorbed or mobilised than is consumed or secreted. On the other hand, a low iron content in the plasma may be due either to iron's being consumed to a particularly great extent in the production of blood corpuscles, or to not much of it being mobilised or, finally, to a resorption that does not cover the losses, even if these are fairly normal. A deviation from the normal in the iron content of the plasma is therefore not always easy to interpret.

As regards the need of iron, then, we can expect a higher content in the plasma, since not only has the capacity of the bone marrow to produce blood corpuscles been reduced, but also the capacity of the liver to absorb iron may possibly also have been reduced. Now, we have found a low iron content in the plasma. This might mean that, in anaemia, less iron than normal is resorbed from the intestine, or that the patients

have a diet poor in iron, which does not allow them to compensate for the normal iron losses. It may also happen that the liver's capacity to absorb iron is lowered in connection with the increase in the urobilin secretion. On the other hand, it is unreasonable to attribute the lowered iron content in the plasma to any great need of iron in the bone marrow, since the latter's activity is probably inhibited. However, it has been possible to show that, after intravenous iron loading in infectious states, the iron leaves the blood stream more rapidly than normal; this is probably because the iron stores tend to absorb more iron than normally, and are consequently well stocked. Less likely is an increased excretion of iron.

If iron is administered, it should in any case not be able to have any advantageous effect on the bone marrow as long as the latter's activity is inhibited — unless the old view is correct, namely that iron had a stimulating action on this activity. On the other hand it is clear that, as soon as the toxic action on the bone marrow is reduced, the addition of iron might have an effect. It is then necessary to repair that iron deficit resulting from the previous production of too few blood corpuscles which may possibly have arisen.

Although the present author is well aware of the danger in an attempt to review the theoretical possibilities which seem to exist, this presentation has been considered to have a motive, since it simplifies the following discussion of the results obtained.

Course of the anaemia.

As the present author has shown earlier on, there is a statistically significant negative correlation between the values for Hb and S.r. In almost all the pathological material, these values run quite contrary to one another. As pointed out in the chapter on the pathological material, the preparations aurodetoxin and detoxin often have an anaemising effect, and there are reasons for thinking that stay in hospital has a similar effect (see the normal material in Chapter IV), although the

Table 52. *Course of the anaemia at the first and the second admittance in polyarthritic cases from Umeå distributed with regard to S.r. in mm/hr.*

$D + \varepsilon(D)$ = Mean of the differences between the figures at first and second admittance $\pm$ standard error of the mean. $\sigma(D)$ = standard deviation of the differences.

	M e n				W o m e n			
	Num. ber	Mean ₁	Mean ₂	$D \pm \varepsilon(D)$	$\sigma(D)$	Num. ber	Mean ₁	$D \pm \varepsilon(D)$
S.r. unchanged (diff. between the figure at the 1st and the 2nd admittance ± 5 for men, and ± 10 mm for women)								
Hb. in %	12	90.0	93.6	$+ 2.7 \pm 2.4$	8.2	18	75.2	$75.4 \pm 0.2 \pm 2.2$
RBC in millions	12	4.85	5.00	$+ 0.15 \pm 0.09$	0.31	18	4.27	$4.33 \pm 0.06 \pm 0.12$
Colour index	12	0.937	0.934	$- 0.003 \pm 0.018$	0.062	18	0.883	$- 0.010 \pm 0.022$
S.r. drops more than 5 mm for men, more than 10 mm for women								
Hb. in %	13	82.6	82.4	$- 0.2 \pm 3.1$	11.3	13	73.6	$73.5 \pm 0.1 \pm 3.2$
RBC in millions	13	4.57	4.56	$- 0.01 \pm 0.15$	0.53	13	4.05	$4.16 \pm 0.11 \pm 0.12$
Colour index	13	0.905	0.903	$- 0.002 \pm 0.024$	0.089	13	0.914	$- 0.032 \pm 0.029$
S.r. rises more than 5 mm for men, more than 10 mm for women								
Hb. in %	3	91.3	85.6	$- 5.7$	—	7	73.3	$- 8.0$
RBC in millions	3	4.96	4.91	$- 0.05$	—	7	4.34	$- 0.29$
Colour index	3	0.926	0.873	$- 0.053$	—	7	0.839	$- 0.028$

pathological material is not fit for to demonstrate this. The first factor to be considered as likely to cause such anaemia is the lack of exercise. That is to say, this factor may play a part primarily in that the blood reserves containing more concentrated blood will to some extent become larger, partly because the reduced need of oxygen may be thought to produce a lowered production of red blood corpuscles. This question has been dealt with more fully in Chapter IV.

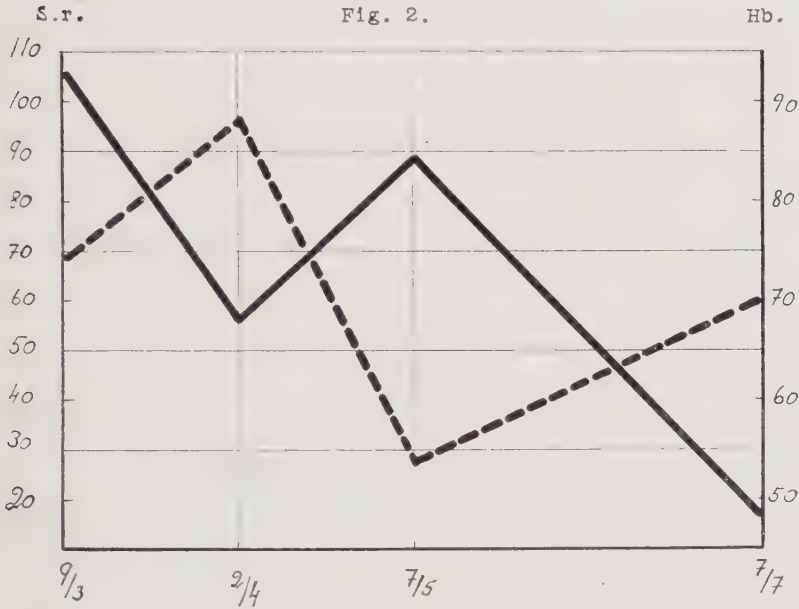
The anaemising effect of the stay in hospital is not possible to determine. It therefore only remains, to study the course of the anaemia on the values on admission of patients treated on several occasions.

We begin by giving, in table 52, the anaemia values in rheumatic subjects at the first occasion for treatment, and at the later one. The material has been grouped according to S.r., since we found this to be the most suitable gauge of the infection, at present. One would expect the anaemia to improve in the group containing the cases where the S.r. changed for the better or remained constant, and to increase in the group where S.r. rose. The cases which had been treated several times, and which we were able to use for this comparison, are however too few to allow of any conclusions. The differences are nowhere significant or probable in respect of their standard error. Nor does a grouping of the cases according to degree of severity (status of the joints) yield any differences which could be used for drawing conclusions. This table is not published.

It should be mentioned that the patients returning for a second treatment are those who, in the first place, had no great improvement in their joint status. There is therefore hardly any reason to expect any very great improvement in the anaemia, if this complaint runs parallel with the infection and the joint symptoms.

It might be interesting to compare the values on admission to and discharge from hospital, but we have not done so here. Data, however, are given in the section on the effect of iron therapy.

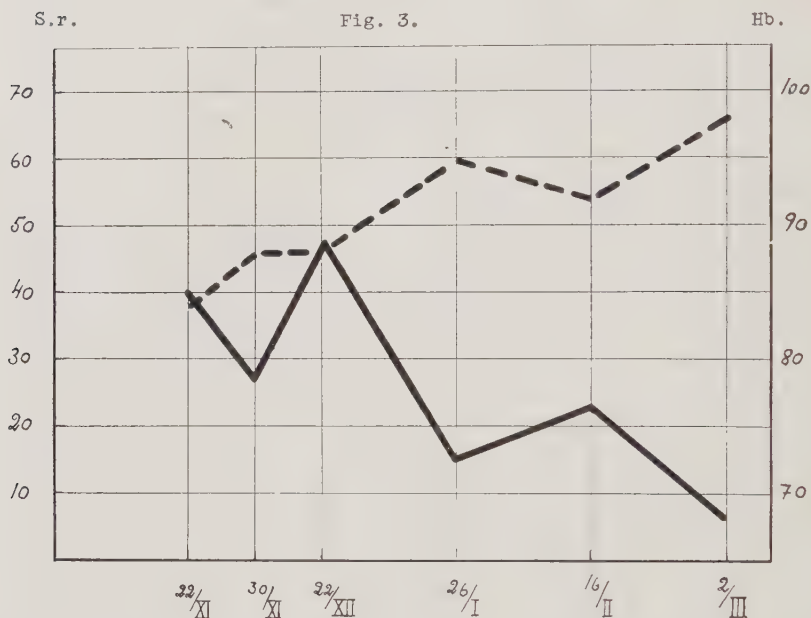
It then only remains to demonstrate the course on single cases. To this end we give some curves showing the course in a number of representative cases. In all the figures the whole line is S.r. and the broken line is Hb.



The case in fig. 2 concerned a 20-year-old woman, who on 4/3 contracted pains in some of her joints (following angina). She was admitted to hospital on 9/3, and found to have pericarditis. She was in bed, usually with a temperature between 38 and 39° C, lower at some periods. About 7/5, her condition became perceptibly worse, with raised temperature and enhanced joint symptoms. Gradually improved, subjectively and objectively. No special treatment for anaemia.

The case in fig. 3 was a middle-aged woman with mediumly severe polyarthritis, who showed considerable improvement during her stay in hospital. No special treatment for anaemia.

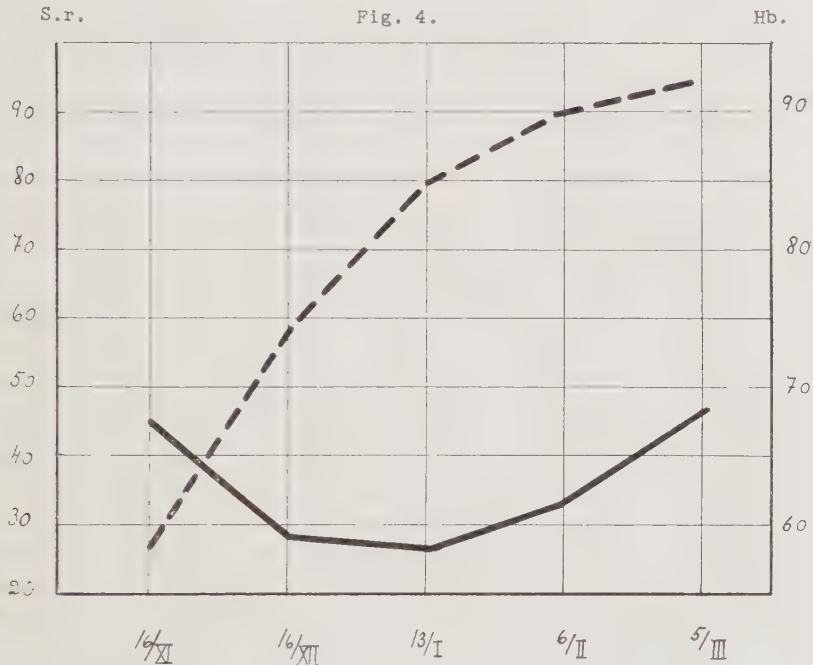
The case in fig. 4 was a middle-aged woman with slight polyarthritis, who improved during her stay in hospital, receiving peroral iron treatment during the entire period of treatment. Here there seems to be reason for supposing that some other factor besides the mere joint disease affected the course, particularly as the S.r. was about the same at admission as at discharge, and the colour index rose from 0.6 to 1.0.



The case in fig. 5 differed from the others in that the Hb value sank at the same time as the S.r. improved. This case was also treated with aurodetoxin, and, as mentioned earlier, the detoxin component in this preparation sometimes causes anaemia.

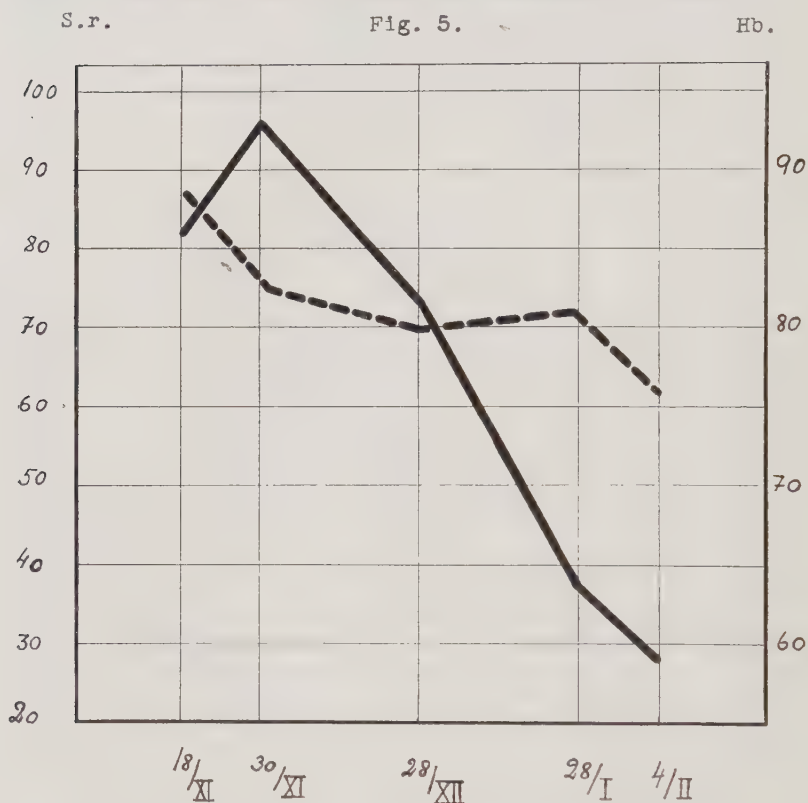
As a matter of fact, the same state of affairs (i.e. that the Hb value falls at the same time as the S.r. falls) obtains just before death; this is most readily seen in cases of pulmonary tuberculosis, where there is reason to suppose that the organism's capacity to react is very much lowered or has nearly ceased to function at all.

These curves have been taken from the present author's earlier works (1937 and 1939), and can be taken to be representative of this material, too, although cases treated with aurodetoxin and detoxin have not been included in the latter. An examination of the material shows isolated cases which differ from the main bulk, and seem most nearly to correspond to the cases set out in fig. 4. Figures for these cases have been tabulated. See page 151.



There are, however, also many cases — especially among the men — that show normal figures for Hb and red blood corpuscles, despite manifest rheumatic infection. In such cases there is reason to suppose the presence of some resistance to the toxic action on the haematopoietic organs. The cause may be genetical or something else. It also seems as if cases with arterial hypertension get anaemia less often than others. This material cannot be dealt with from that angle. Further, it seems

as if cases of hepatitis, which in addition are characterised by high serum iron, do not often contract anaemia, in spite of severe and long-drawn-out infections. Naturally, further observations are required to establish these matters firmly.



An examination of the material gave reason to suppose that a factor other than the rheumatic infection helped to cause the anaemia in the cases on next page. The material consists of 3 men and 12 women. While the other cases show, on the whole, the usual phenomenon of the Hb values rising and falling contrary to the S.r., these cases show rising Hb values at the same time as mainly static values for S.r. The S.r. is often lowered, but the initial value most frequently falls within the limits for the normal (exceptions are 189/40 and 210/40, but S.r. is not high there, either).

No.	Age in years	Duration in mths	Course	Joint status	Male.		D.	Hb	RBC	C.I.	D.	S.I.
					S.r.	Therapy in days						
72/41	27	72	A	D	5	24	21/3	63	4.35	0.72	8/4	61
					3		12/5	85	4.96	0.86	12/5	68
242/42	22	2	A	D	3	49	29/9	78	4.41	0.80	6/10	173
					6		23/11	89	4.58	0.97		240
												245
256/42	24	60	A	D	3	60	16/10	80	4.23	0.95		
							7/12	98	5.18	0.95		
Female.												
28/40	31	25(7)	A	D	8	0	18/1	68	3.67	0.93	7/2	83
					6		14/3	83	4.23	0.98		
143/40	20	36	B	D	7	49	31/5	68	3.95	0.86		
					3		26/8	83	4.90	0.85		
179/40	17	6	A	D	12	0	16/7	74	4.36	0.85		
					4		9/9	85	4.43	0.96		
189/40	26	48(7)	A	D	18	23	29/7	68	3.56	0.96		
					10		16/9	80	4.80	0.83		
210/40	18	19	B	E	27	83	26/8	70	4.67	0.75	6/9	89
					20		4/11	85	4.48	0.85		
319/40	43	10	A	E	11	60	21/12	58	4.33	0.67	27/12	49
					11		17/3	75	4.30	0.87	10/2	95
102/41	40	76(7)	A	D	10	50	25/4	58	4.25	0.68	29/4	33
					8		16/6	69	4.41	0.78		
211/42	26	67(12)	A	D	10	87	25/8	63	3.77	0.84	9/10	55
					3		16/11	80	4.19	0.97	20/11	75
226/42	49	36(5)	D	E	28	83	8/9	61	3.84	0.79	11/9	65
					29		30/11	75	4.16	0.90	4/12	45
233/42	44	108(9)	B	E	9	43	17/9	76	4.26	0.89	28/9	85
					15		9/11	90	4.54	0.99	10/11	96
254/42	36	42(6)	B	E	9	47	13/10	61	4.10	0.74	23/10	45
					4		7/12	76	4.58	0.83	9/12	81
268/42	47	96	A	E	10	59	4/11	51	4.19	0.61	8/11	86
					5		21/12	68	4.24	0.80		

Column 1 indicates the registration number of the case. The figure in brackets under the duration gives the period in months since the last exacerbation. Course = type of course before admission. Joint status = joint status at admission. Duration of the therapy applies to iron therapy (preparation used was ferrosi tartr. 1 gm $\times$ 3, or pil. ferrosi chlor. 2—3 gm $\times$ 3, corresponding to 0.45—0.68 gm iron chloride daily). C.I. = colour index, S.I. = serum iron, D = data of the observations.

Common to all these cases is a definite anaemia, combined with a usually fairly mild course for the joint disease and not very marked objective symptoms, either in the form of joint changes or high S.r. The colour index is usually low. The serum iron is also low, but not markedly so. Iron loading was performed only in Case 242/42.

When assessing anaemias in infectious states, particularly the above exceptions, there are various possibilities to choose from. There may be

- 1) a purely infectious anaemia, with inhibition of the production of Hb and red blood corpuscles,

- 2) cases of infection which happen to coincide with a pronounced form of iron deficiency anaemia (lowered saturation of Hb in the diminished red blood cells),

- 3) cases liable to a hypochromic reaction due to iron deficiency,

- 4) cases which, for reasons other than iron deficiency, are liable to a hypochromic reaction (greater inhibition of the production of Hb than of the stroma of the red blood corpuscles), and which contract an infectious anaemia of a more or less hypochromic type.

As the cited exceptions are mild cases with normal or only slightly raised S.r., there is reason to suppose that they belong in the main to groups 2), 3), or 4), whereas it does not seem possible to say definitely to which of these groups the single case belongs.

The cases coming under groups 2) and 3) should logically respond to iron therapy, while it is less likely that the cases belonging to group 4) would be improved by such a process.

Most of the cited exceptions were given iron therapy. However, 2 cases improved without any such dosage, showing clearly that these cases, too, may show spontaneous recovery from the anaemia.

Clinical viewpoints, however, would seem to dictate iron therapy in groups 2) and 3). Group 4) will, in practice, come under the same head, since it does not seem possible to separate this group from groups 2) and 3). As will be shown in the chapter on iron therapy, group 1) does not respond to iron therapy. In more severely infected cases, however, it is probably not always possible to determine whether the lowered Hb production is due to iron deficiency + infection, or to the infection alone. Nevertheless, if the infection is slight and the anaemia intense, it would be reasonable to give treatment for iron deficiency. All the same, we cannot quite rule out the possibility that there may be isolated cases of active rheumatic infection which for some reason does not give raised S.r., but does give anaemia.

Practically speaking, there can be nothing wrong in giving iron to these anaemic cases, but there is reason to confine such dosage to cases where the degree of anaemia does not tally with what might be expected according to the infection.

Peroral iron loading of cases with rheumatoid arthritis before and after iron therapy.

Wherever there is anaemia, we can always say that there is a lack of iron in the body, inasmuch as the amount of iron represented by the red blood corpuscles, and the haemoglobin they contain, is less than normal. If the anaemia is any way pronounced, the organism should have a tendency to cover this iron deficit, and should do this more quickly when extra iron is added to the diet. As is known, this is the reason for iron therapy in cases of anaemia. To see whether this is what really happens, iron-loading tests can be made before and after iron therapy, thus testing whether the extra iron actually is absorbed into the body; if it is, the immediate result should be that the serum iron is raised and the reaction after iron loading is normalised.

To investigate these questions, the present author has carried out iron loading on 10 men and 23 women, all suffering from rheumatoid arthritis of varying degrees of severity, before and

2 days after the end of iron treatment. The preparation used was 1 gm ferrosi tartras thrice daily. The treatment lasted 40-60 days. The iron was given perorally in the usual manner. The results of the investigation are outlined in the table 53.

Table 53. *Serum iron in iron loadings before and after the iron treatment. The pathological cases from Umeå.*

$D \pm \varepsilon(D)$ = Mean of the differences between figures before and after treatment $\pm$ standard error of the mean.

	Num- ber	Mean before treatment	Mean after treat- ment	$D \pm \varepsilon(D)$	$\sigma(D)$
M e n					
Before the test	10	120.6	113.6	— 7.0 ± 12.6	39.9
2 hours after	10	150.4	131.5	— 18.9 ± 22.7	71.8
4 hours after	10	149.3	138.2	— 11.1 ± 26.7	84.5
W o m e n					
Before the test	23	80.5	81.5	+ 1.0 ± 6.8	32.8
2 hours after	23	118.9	111.0	— 7.9 ± 9.7	46.3
4 hours after	23	122.9	104.3	— 18.6 ± 12.0	57.6

We see that the serum iron values before iron loading are not materially affected by the prolonged iron treatment, and that the same values 2 and 4 hours respectively after loading are, if anything, lower than before treatment, both in men and in women (this agrees with what Vahlquist showed in 1944 on normal subjects). However, there are no statistically probable or significant differences.

The joint status of the cases has been divided in table 54, to show which subjects were loaded with iron before and after iron treatment. It also compares the joint status on admission and at discharge, i.e. whether the case improved, remained the same, or became worse during treatment. It is seen that most of them improved, which — in conformity with what has been shown earlier — should mean that the serum iron is consequently raised.

Table 54. *Joint status and course during the stay at the hospital for polyarthritic cases from Umeå who have had iron treatment and iron loading before and after the treatment.*

Joint status	Course between admittance and discharge			
	Improved	Unchanged	Impaired	Total
M e n				
D.	3	—	—	3
E.	4	—	—	4
F.	2	1	—	3
Total	9	1	—	10
W o m e n				
D.	1	—	—	1
E.	10	6	1	17
F.	3	1	1	5
Total	14	7	2	23

The rise in the serum iron obtained after a peroral loading is certainly due to the fact that the high iron content in the alimentary canal, as it were, forces iron into the blood plasma. A more moderate iron content causes no change in the blood plasma — that is to say that, provided conditions are normal, the body absorbs no or very little iron when the iron content of the diet is more normal. The situation is quite another in anaemia. There, as mentioned above, the body can be expected to absorb iron. This absorption should, of course, be far greater before treatment than after, in so far as any iron requirements that may be present will be met by the treatment. After the treatment has been going on for some time, the body should not have any tendency towards absorbing more iron. We should therefore expect to get a lower effect from loading after some time of treatment. Our inability to produce a difference of this kind may, of course, be due to the fact that the material was too small. On the other hand, it should be mentioned that if any very great difference were in question, it would have appeared even in this small material.

A factor which has bearing on these experiments is that the capacity of the alimentary canal to let iron through may be affected by disease. If the capacity to absorb iron purely locally is upset, the effect of the treatment may be little or none. In this case the iron loading can be expected to cause a subnormal rise in the iron content of the blood serum. As far as can be judged from the available figures, the effect of iron loading is far smaller in these cases. This might, of course, be due to an inability to resorb iron.

However, we have shown by experiments with intravenous iron loading that, in cases of rheumatic infection, the iron leaves the blood stream more quickly than normally. It is not inconceivable that this happens after peroral loading also, causing lowered values for the serum iron at the time of loading. Our material does not allow any definite conclusions as to this, so that the question of whether there is lowered resorption or quicker transport of the iron out of the blood stream must remain open. See also the short discussion in chapter X.

Effect of iron therapy.

As mentioned at the beginning of this chapter, it is hardly likely that iron therapy affects haematopoiesis in these conditions, as long as the rheumatic complaint inhibits the activity of the haematopoietic organs — unless, as was previously believed to be the case, iron *as such* has a stimulating action on the bone marrow. It is furthermore possible that the iron stores might be insufficient during the period for repairs, when the anaemia is subsiding, to satisfy the abnormally increased need of iron. There may also be cases where a rheumatic infection and an iron deficit coincide, since both these disease states are relatively common. In these cases iron therapy should be of importance.

Opinions have differed as to the effect of iron therapy in infectious anaemias. Good results have sometimes been claimed — naturally enough, if one takes into account the tendency of these anaemias to subside of their own accord (cf. present author's works of 1937 and 1939) when the basic disease

improves. Latterly, however, observations of single cases have led most investigators to the conclusion that anaemias accompanying infections very seldom respond to anti-anaemic therapy. Nevertheless, Heilmeyer and co-workers (1937) considered that a iron deficit was present, due to the low serum iron and the hypochromic nature of the anaemias. Skouge (1939) seems inclined to accept this view, though it is only backed up by one single published case, which probably subsided of its own accord during iron therapy. Dahl (1944) and Löfgren (1945) have also observed the frequent occurrence of hypochromia in these anaemias, but are aware of the poor results of iron treatment.

Cartwright, Wintrobe and co-workers describe, in their turn, an infected case who received intravenous injections of a total of 1.5 gm iron ascorbate for 30 days, without any sure effect on serum iron, erythrocyte protoporphyrine or haemotocrite. Another case was given the same dosage for 20 days, with ferrosulphate and copper sulphate per os in addition, without any effect as regards the above-mentioned matters. The same was true of a further case, given the Vitamin B complex as well as iron ascorbate, and of other cases given penicillin, amigen, globin, cystine, methionine and crude liver extract (Wilson).

For the number of treated cases in my material, and for the iron preparations used and the length of treatment, see tables 55 and 56. The iron dosage was for ferros. tartr. 1 gm $\times$ 3, for ferros. chlor. 0.15 — 0.23 gm $\times$ 3 and for ferr. reduct. 1 gm $\times$ 3.

Table 55. *The polyarthritic cases from Umeå distributed according to the preparation used during the iron treatment.*

Preparation		Number of cases	
M e n	Tabl. ferros. tartr.		13
	Pil. ferros. chlor.		7
	Total		20
W o m e n	Tabl. ferros. tartr.		42
	Ferr. reduct.		1
	Pil. ferros. chlor.		49
Total			92

Table 56. *The polyarthritic cases from Umeå distributed according to duration (in days) of the iron treatment.*

Days	M e n			W o m e n			
	Tabl. ferros. tartr.	Pil. ferros. chlor.	Total	Tabl. ferros. tartr.	Pil. ferros. chlor.	Ferrum reduc- tum	Total
1—15	1	—	1	1	7	—	8
16—30	2	—	2	—	9	1	10
31—45	4	—	4	5	6	—	11
46—60	4	1	6	18	16	—	34
61—75	1	1	2	2	3	—	5
76—90	1	1	2	7	5	—	12
91—105	—	2	2	2	—	—	2
106—120	1	—	1	2	2	—	4
121—135	—	—	—	2	1	—	3
136—150	—	—	—	—	1	—	1
Total	14	5 ¹	19 ¹	39 ²	50	1	90 ²

One man and 2 women became 2 of the preparations, 1 woman receiving campoferron (Bayer) as well as the iron tartrate tablets, without any noticeable effect on the blood values.

When tabulating the subjects who did and did not receive iron, I have made a great point of allowing for the spontaneous recovery which occurs with the improvement of the main disease. On this account, particular heed has been paid to the sedimentation rate, since we have shown already that there is a statistically significant negative correlation between Hb and S.r., and the latter can be considered as the best gauge we have at present of the strength of the infection.

Table 57 outlines the total material of treated and non-treated cases. As appears, the cases not receiving iron predominate, particularly as regards the men. The values on admission for the cases treated with iron are considerably lower for Hb, RBC and colour index, and higher for S.r., than the corresponding values for non-treated cases. The explanation of this is that the anaemic cases were the first objects of iron treatment. The

¹ In addition 1 case without information about duration of treatment.

² In addition 2 cases without information about duration of treatment.

small number of non-treated cases investigated as regards reticulocytes and the diameter of the red blood corpuscles makes it impossible to say anything about these two aspects.

Table 57. *Different laboratory figures at admission and at discharge in polyarthritic cases from Umeå with or without iron treatment.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	With iron treatment			Without iron treatment		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
Figures at admission. Men.						
Hb. in %	20	79.90 ± 2.24	10.02	110	88.32 ± 0.87	9.09
RBC in millions	20	4.368 ± 0.075	0.336	110	4.769 ± 0.044	0.458
S.r. mm/hr.	20	36.8 ± 7.3	32.8	110	18.0 ± 1.9	19.8
Colour index	20	0.8775 ± 0.0221	0.0990	110	0.9308 ± 0.0058	0.0608
Reticulocytes	10	$5.3(\pm 1.5)$	4.6	5	2.8	—
RBC, diameter	10	$7.693(\pm 0.034)$	0.107	5	7.8	—
Figures at discharge. Men.						
Hb.	20	76.90 ± 2.13	9.52	110	89.30 ± 0.77	8.07
RBC	20	4.539 ± 0.074	0.329	110	4.809 ± 0.037	0.388
S.r.	20	28.9 ± 6.8	30.5	110	11.0 ± 1.3	13.6
Colour index	20	0.8780 ± 0.0169	0.0755	110	0.9284 ± 0.0042	0.0436
Reticulocytes	10	$7.9(\pm 2.0)$	6.2	5	5.0	—
RBC, diameter	10	$7.748(\pm 0.037)$	0.118	5	7.8	—
Figures at admission. Women.						
Hb.	92	70.32 ± 0.83	7.95	115	79.17 ± 0.68	7.26
RBC	92	4.160 ± 0.037	0.352	115	4.312 ± 0.029	0.307
S.r.	92	27.0 ± 2.3	21.9	115	19.8 ± 1.6	17.0
Colour index	92	0.8484 ± 0.0086	0.0825	115	0.9184 ± 0.0054	0.0583
Reticulocytes	30	8.0 ± 1.1	6.0	3	6.3	—
RBC, diameter	31	7.665 ± 0.028	0.153	2	7.7	—
Figures at discharge. Women.						
Hb.	92	72.67 ± 0.91	8.69	115	78.38 ± 0.57	6.10
RBC	92	4.245 ± 0.031	0.294	115	4.304 ± 0.023	0.243
S.r.	92	16.9 ± 1.6	15.1	115	13.9 ± 1.3	13.8
Colour index	92	0.8616 ± 0.0070	0.0671	115	0.9114 ± 0.0051	0.0548
Reticulocytes	30	7.2 ± 1.1	6.1	2	7.5	—
RBC, diameter	31	7.672 ± 0.032	0.178	1	8.0	—

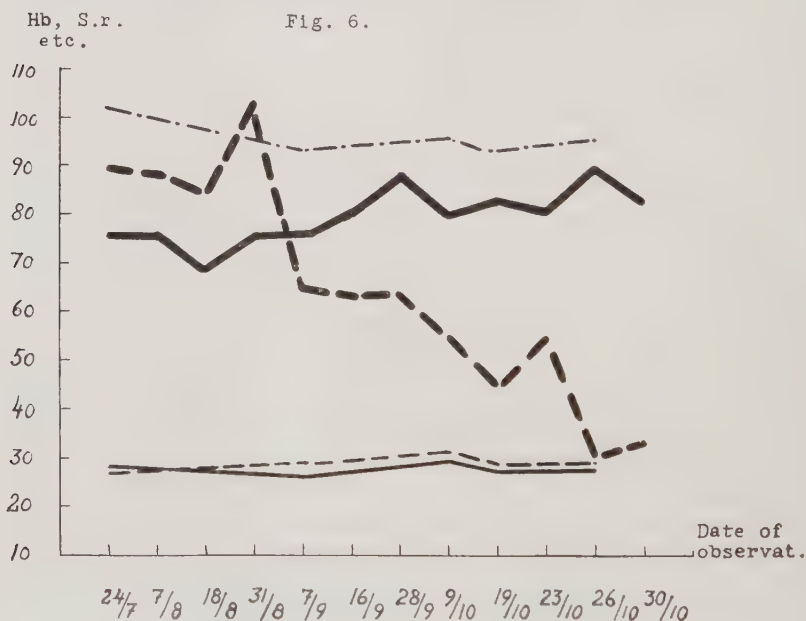
Having found that most of the anaemic cases have been treated with different iron preparations, often over a long

period, we can proceed to seeing whether this therapy had any effect. This should be of interest since, as far as I have been able to discover, this matter has not been studied on any large infected material, with allowances made for spontaneous recovery. The iron treatment does not seem to have any effect either on the Hb values, the number of red blood corpuscles, the colour index, the diameter of the red blood corpuscles or the number of reticulocytes.

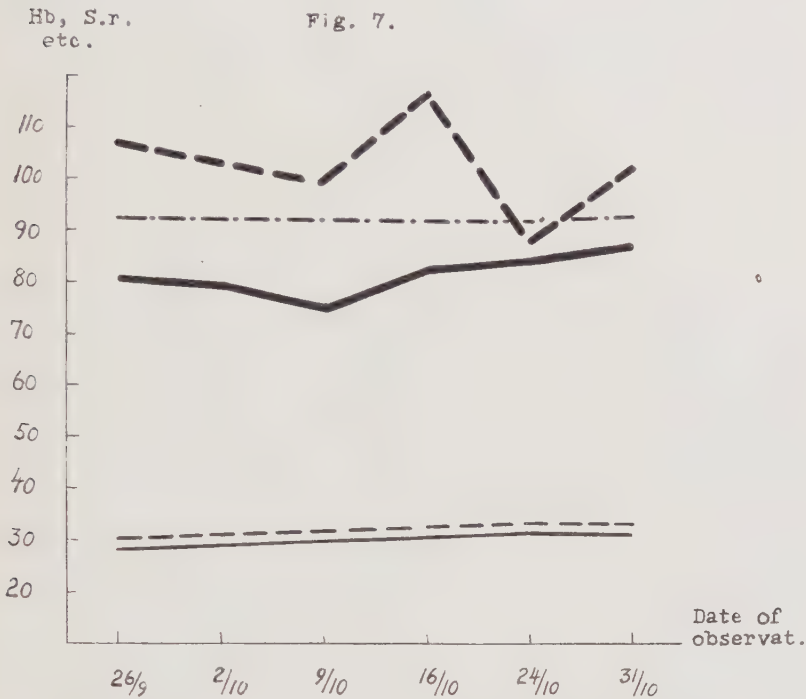
This argues against the presence of some iron deficiency factor as cause of the anaemia — unless there is a disturbance in the resorption of iron from the gastro-intestinal canal.

To see whether this is so, the present author gave each of 2 patients 200 mgm of iron as iron and ammonium citrate in 20 intravenous injections. The results are shown in the following diagrams. In both the following lines are used:

- Haemoglobin in per cent
- - - - - Sedimentation rate in mm/hr.
- . — . — Mean corpuscular volume
- Mean haemoglobin concentration
- - - - - Mean corpuscular haemoglobin concentration.



The case in fig. 6 was a 30-year-old man, who had had joint trouble for 22 months. Type of course was B, and joint status C.



The case in fig. 7 was a 58-year-old man, who had had joint trouble for about 10 years. Type of course B, joint status C.

Neither of them had very bad anaemia. I would attribute the improvement in the anaemia rather to the reduction of S.r., and therewith of the decrease of the intensity of the infection, than to the iron therapy. Needless to say, a more extensive study is required to determine the true state of affairs.

A further table (58) has been drawn up to show the female cases receiving iron. Here, the sedimentation rate has governed the grouping in that cases where it remained unchanged (± 5 mm/hr) or became worse by more than 5 mm/hr have been made into one group, which is compared with the cases where S.r. improved by more than 5 mm/hr. The first two had to be made into one owing to the fewness of the cases that got worse.

Table 58. *Polyarthritic women from Umed who got iron irtreatment distributed with regard to S.r. during the treatment.*

$D \pm \varepsilon(D)$ = Mean of the differences between figures at admission and discharge $\pm$ standard error of the mean. $\sigma(D)$ = Standard deviation of the difference.

	Num- ber	Figure at admis- sion = M_1	Figure at discharge = M_2	$D \pm \varepsilon(D)$	$\sigma(D)$
Cases in whom S.r. remained unchanged (± 5 mm) or in whom S.r. increased more than 5 mm/hr.					
Hb. in %	43	72.12	73.72	— 1.60 ± 1.30	8.55
RBC in millions	43	4.229	4.266	— 0.037 ± 0.056	0.366
S.r. mm/hr.	43	16.2	18.9	— 2.7 ± 1.7	10.9
Colour index	43	0.854	0.866	— 0.012 ± 0.011	0.075
Reticulocytes	16	7.06	7.81	— 0.75 ± 2.19	8.78
RBC, diameter	17	7.6412	7.6518	— 0.0106 ± 0.0552	0.2278
Cases in whom S.r. decreased more than 5 mm/hr.					
Hb.	49	68.51	72.69	— 4.18 ± 0.96	6.70
RBC	49	4.121	4.241	— 0.120 ± 0.057	0.399
S.r.	49	37.9	15.2	+ 22.6 ± 2.8	19.9
Colour index	49	0.836	0.856	— 0.020 ± 0.011	0.079
Reticulocytes	14	9.00	6.50	+ 2.50 ± 2.40	8.99
RBC, diameter	14	7.6986	7.6957	+ 0.0029 ± 0.0437	0.1635

The group where S.r. is unchanged or has become worse shows no statistically probable or significant differences concerning the observed blood factors. The cases with S.r. improved, on the other hand, show a statistically significant rise in the Hb values between admission and discharge.

This investigation shows that, on the whole, it is the course of the basic disease and not the iron therapy that determines the height of the Hb.

Isolated cases, which an examination of this material enabled us to take to be exceptions from this rule, have been described earlier on in this chapter, where also an account is given of how the anaemias occurring in the infectious states could be divided.

CHAPTER XII.

The relation between Hb and RBC in Upsala normal and pathological material.

Unfortunately, haemocrite determinations were not made in the Umeå material. For this reason, the present author decided to draw up a new material (normal material and pathological material) for studies of the mean corpuscular volume (M.C.V.), mean corpuscular haemoglobin (M.C.H.), and mean corpuscular haemoglobin concentration (M.C.H.C.), since it seemed possible that these absolute figures for the relation between haemoglobin and red blood corpuscles in a larger material might add to our knowledge of the nature of the anaemias observed in rheumatic infections. This new material has been called the Upsala material.

The Upsala normal material consists of 58 healthy men and 64 healthy women. Most of the men were soldiers, and the women were nursing staff and Swedish ATS.

The methods of investigation been described in Chap. III, and a comparison between Upsala and Umeå normal materials made in Chap. IV, which also contains a discussion of the differences then observed between the two. Certain normal figures observed earlier on in the literature have been described in Chap. II, and the relation between Hb and red blood corpuscles in normal and infected material also is reported in Chap. II. Table 59 outlines the Upsala normal material.

Table 59. *Different laboratory figures and differences between men and women in the normal cases from Uppsala.*

$M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	M e n			W o m e n			Diff.
	Number	$M \pm \epsilon(M)$	σ	Num- ber	$M \pm \epsilon(M)$	σ	
Hb. in %	58	104.09 ± 0.72	5.47	64	89.03 ± 0.84	6.71	15.06 ± 1.11
RBC in millions	58	5.260 ± 0.056	0.423	64	4.344 ± 0.053	0.421	0.916 ± 0.077
Hematocrite	58	44.93 ± 0.33	2.50	64	40.15 ± 0.25	2.00	4.78 ± 0.41
S.r. in mm/hr.	58	3.40 ± 0.29	2.23	63	8.83 ± 0.55	4.35	5.43 ± 0.62
Colour index	58	0.995 ± 0.011	0.082	64	1.031 ± 0.012	0.098	-0.036 ± 0.016
M.C.H.	57	30.43 ± 0.28	2.12	64	31.54 ± 0.38	3.01	-1.11 ± 0.47
M.C.V.	57	89.06 ± 0.66	4.98	64	92.26 ± 0.96	7.70	-3.20 ± 1.17
M.C.H.C.	57	35.53 ± 0.23	1.75	64	33.97 ± 0.28	2.24	1.56 ± 0.36

There are statistically significant sex differences for Hb, RBC, haemotocrite, S.r., and M.C.H.C. (mean corpuscular haemoglobin concentration), and a statistically probable difference for M.C.V. (mean corpuscular volume). This means that the men have higher values than the women for Hb, RBC, haemotocrite and S.r., and that the men in this normal material probably have somewhat smaller blood corpuscles than the women, and a somewhat greater saturation of haemoglobin in the single red corpuscle. A tendency towards the same sex difference seems probable for the normal materials collected earlier, which are presented in table 8, although — to my knowledge — this tendency has not been pointed out previously. The unusually clear difference here between male and female normal material may, as mentioned earlier on, be explained by the fact that this male normal material of soldiers differs from the normal material obtained when investigating nursing staff and patients free from diseases which might be thought to affect the values for Hb and RBC. From certain angles, therefore, this normal material may be said to be unfortunately chosen, since it represents 'far too healthy persons'. On the other hand, we might claim that a comparison between a normal material of this kind and an infected material will be more valuable than a comparison with a normal material that does not reach very high normal blood values.

The pathological Upsala material has been described more fully in the Chapter IV. Here, the total pathological Upsala material (41 men and 56 women) and the difference between the sexes have been outlined in table 60.

The difference between men and women in the total pathological material is statistically significant as regards Hb, red blood corpuscles and haemotocrite, but the other investigated values yield no statistically probable or significant differences. This may of course be due to a different distribution of cases of different degrees of severity in the materials. This aspect will be studied in the various groups.

The results of comparing the Upsala normal material with the total pathological material, and calculating the differences, are found in table 61.

Table 60. *Different laboratory figures and differences between men and women at admittance in the polyarthritic cases from Uppsala.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	M e n			W o m e n			Diff.
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ	
Hb. in %	41	86.3 ± 1.5	9.6	56	78.2 ± 1.4	10.2	8.1 ± 2.0
RBC in millions	41	4.524 ± 0.064	0.408	56	4.192 ± 0.062	0.463	0.332 ± 0.089
S.r. in mm/hr.	41	41.82 ± 0.67	4.27	56	37.75 ± 0.54	4.05	4.07 ± 0.86
Hematocrite	41	52.6 ± 5.2	33.5	56	53.3 ± 4.3	32.0	-0.7 ± 6.8
Colour index	41	0.955 ± 0.013	0.082	56	0.936 ± 0.014	0.108	0.019 ± 0.019
M.C.H.	41	29.38 ± 0.41	2.62	56	28.89 ± 0.46	3.46	0.49 ± 0.62
M.C.V.	41	92.2 ± 1.1	7.0	56	91.0 ± 1.2	9.0	1.2 ± 1.6
M.C.H.C.	41	31.68 ± 0.32	2.07	56	31.71 ± 0.35	2.61	-0.03 ± 0.47

Table 61. *Differences between the normal cases and the polyarthritic cases from Uppsala in regard to different laboratory figures.*

	Diff. between the normal cases and the polyarthritic cases from Uppsala	
	M e n	W o m e n
Hb. in %	17.8 ± 1.7	10.9 ± 1.6
RBC in millions	0.736 ± 0.085	0.152 ± 0.082
Hematocrite	3.11 ± 0.75	2.40 ± 0.60
S.r.	-49.2 ± 5.2	-44.5 ± 4.3
Colour index	0.040 ± 0.017	0.095 ± 0.018
M.C.H.	1.05 ± 0.50	2.65 ± 0.60
M.C.V.	-3.2 ± 1.3	1.3 ± 1.5
M.C.H.C.	3.85 ± 0.39	2.26 ± 0.45

There are statistically significant differences among the men for Hb, RBC, haematocrite, S.r., and M.C.H.C., and among the women for Hb, haematocrite, S.r., colour index, M.C.H., and M.C.H.C. This means that, in the men, the rheumatic infection lowers the values for Hb and the red blood corpuscles and raises the sedimentation rate, while in the women it lowers the values for Hb and colour index and raises the S.r., the women retaining the number of red blood corpuscles better. For the absolute figures for the relation between Hb and red blood corpuscles, these observations imply that the saturation of Hb (M.C.H.C.) in the red blood blood corpuscles both of men and of women is less than normal: this tallies with the view we voiced previously — namely that there is an inhibition of haemoglobin production in infectious conditions. The fact that M.C.H., and therewith the colour index, is lowered in the women but not in the men suggests that the size of the corpuscles is retained better among the former than among the latter. The lack of any probable or significant difference for M.C.V. (though the difference approaches statistical significance among the men) between normal material and pathological material perhaps suggests that there is no real change of *size* in the blood corpuscles, but a change of *form* towards increased thickness (cf. Chap. VIII), and that the red corpuscle is altered, not quantitatively but qualitatively. It also indicates that, when

under the influence of a toxin, the bone marrow retains its capacity to form the stroma of the red corpuscle better than its capacity to form haemoglobin. However, this material is not very large, and a bigger one is required to prove these matters; nevertheless, these investigations must be said to point in the direction indicated.

The results of examining the materials according to type of course (actual progression tendency) are shown in Tables 62 and 63. For the symbols, see the chapter on the material. Here, too, it should be mentioned that the material is fairly small. Cases with fever have, as usual, been relegated to group C, and this material also contains cases with rheumatic fever, which may possibly affect the result.

There are no statistically probable or significant differences for M.C.V., M.C.H., or M.C.H.C. between the different groups showing type of course, either for men or women; on the other hand, the men show a statistically probable difference between groups B and C for red blood corpuscles, and between groups A and C for haematocrite; further, they show a statistically significant difference for S.r. between groups A and C and B and C. For the women, there is a statistically significant difference for Hb, RBC and S.r. between groups A and C, and for RBC between B and C; they show statistically significant differences for Hb between groups B and C, and for S.r. between groups A and B.

If the material is divided up according to joint status groups (actual activity), the distribution is fairly even for the men; for the women, however, it is singularly uneven, so that groups D and F are far too small for statistical treatment. See Table 64.

The difference between the values in the different joint status groups can consequently only be calculated for the men. See Table 65.

There are statistically significant differences for Hb and S.r. between groups D and E and D and F, and for haematocrite between groups D and F. For the absolute figures for the relation between Hb and RBC, there are no statistically significant or probable differences.

Table 62. *Different laboratory figures in the polyarthritic cases from Uppsala, distributed according to type of course before admittance.*

$M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

Type of course before admittance									
	A			B			C		
	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ	Num- ber	$M \pm \varepsilon(M)$	σ
M e n									
Hb. in %	14	90.8 $\pm$ 2.1	7.8	13	84.9 $\pm$ 2.6	9.3	14	83.1 $\pm$ 2.8	10.3
RBC in millions	14	4.622 $\pm$ 0.125	0.467	13	4.654 $\pm$ 0.091	0.329	14	4.306 $\pm$ 0.092	0.344
Hematocrite	14	44.32 $\pm$ 1.08	4.04	13	41.38 $\pm$ 0.71	2.58	14	39.71 $\pm$ 1.25	4.69
Sr. in mm/br.	14	29.7 $\pm$ 6.2	23.3	13	45.6 $\pm$ 3.4	26.5	14	82.0 $\pm$ 7.2	26.8
Colour index	14	0.984 $\pm$ 0.015	0.055	13	0.913 $\pm$ 0.026	0.094	14	0.965 $\pm$ 0.022	0.083
M.C.H.	14	29.74 $\pm$ 0.63	2.37	13	28.18 $\pm$ 0.72	2.59	14	30.12 $\pm$ 0.71	2.66
M.C.V.	14	94.8 $\pm$ 2.0	7.5	13	89.3 $\pm$ 1.9	7.0	14	92.4 $\pm$ 1.6	6.0
M.C.H.C.	14	31.60 $\pm$ 0.50	1.87	13	31.57 $\pm$ 0.58	2.11	14	31.85 $\pm$ 0.63	2.36
W o m e n									
Hb. in %	17	82.8 $\pm$ 2.1	8.7	20	80.2 $\pm$ 1.7	7.7	19	71.9 $\pm$ 2.6	11.4
RBC in millions	17	4.415 $\pm$ 0.118	0.488	20	4.282 $\pm$ 0.068	0.304	19	3.898 $\pm$ 0.105	0.458
Hematocrite	17	39.74 $\pm$ 0.80	3.31	20	38.08 $\pm$ 0.89	3.96	19	35.10 $\pm$ 1.71	7.45
Sr.	17	28.6 $\pm$ 4.4	18.1	20	45.9 $\pm$ 5.3	23.8	19	83.3 $\pm$ 6.2	26.9
Colour index	17	0.943 $\pm$ 0.024	0.099	20	0.940 $\pm$ 0.023	0.104	19	0.926 $\pm$ 0.030	0.130
M.C.H.	17	28.88 $\pm$ 0.73	3.02	20	29.00 $\pm$ 0.66	2.94	19	28.80 $\pm$ 1.02	4.46
M.C.V.	17	90.4 $\pm$ 2.0	8.3	20	89.2 $\pm$ 2.1	9.4	19	93.5 $\pm$ 2.1	9.2
M.C.H.C.	17	31.79 $\pm$ 0.43	1.76	20	32.43 $\pm$ 0.60	2.69	19	30.87 $\pm$ 0.71	3.09

Table 63. Differences between laboratory figures in polyarthritic cases from Uppsala with different type of course.

	Difference between		
	A — B	A — C	B — C
M e n			
Hb. in %	5.9 ± 3.3	7.7 ± 3.5	1.8 ± 3.8
RBC in millions	-0.032 ± 0.155	0.316 ± 0.155	0.348 ± 0.129
Hematocrite	2.9 ± 1.3	4.6 ± 1.7	1.7 ± 1.4
S.r. in mm/hr.	-15.9 ± 7.1	-52.3 ± 9.5	-36.4 ± 7.9
Colour index	0.071 ± 0.030	0.019 ± 0.027	-0.052 ± 0.034
M.C.H.	1.56 ± 0.96	-0.38 ± 0.95	-1.94 ± 1.01
M.C.V.	5.6 ± 2.8	2.5 ± 2.6	3.1 ± 2.5
M.C.H.C.	0.03 ± 0.77	-0.25 ± 0.80	-0.28 ± 0.86
W o m e n			
Hb. in %	2.6 ± 2.7	10.9 ± 3.3	8.3 ± 3.1
RBC in millions	0.13 ± 0.14	0.52 ± 0.16	0.38 ± 0.13
Hematocrite	1.7 ± 1.2	4.6 ± 1.9	3.0 ± 1.9
S.r. in mm/hr.	-17.3 ± 6.9	-54.7 ± 7.6	-37.4 ± 8.2
Colour index	0.003 ± 0.033	0.017 ± 0.038	0.014 ± 0.038
M.C.H.	-0.12 ± 0.98	0.08 ± 1.25	0.20 ± 1.21
M.C.V.	1.2 ± 2.9	-3.1 ± 2.9	-4.3 ± 3.0
M.C.H.C.	-0.64 ± 0.74	0.92 ± 0.83	1.56 ± 0.93

Dividing the material according to S.r. (< 10 and > 10 mm/hr for the men, and ≤ 30 and > 30 mm/hr for the women) we find a more even distribution among the women. See Table 66.

The male material is so unevenly distributed that no calculation can be made of the differences between the different groups. If one can venture to judge from the figures quoted, there is fairly good agreement between the male and the female material.

Table 64. Different laboratory figures in the pathological cases from Uppsala distributed according to joint status.

M $\pm$ ϵ (M) = mean $\pm$ standard error of the mean; σ = standard deviation.									
Joint status at admittance									
D				E				F	
Num- ber	M $\pm$ ϵ (M)	σ	Num- ber	M $\pm$ ϵ (M)	σ	Num- ber	M $\pm$ ϵ (M)	σ	
M e n									
Hb, in %	12	94.0 $\pm$ 2.0	7.1	14	84.9 $\pm$ 2.2	8.1	15	81.4 $\pm$ 2.3	9.1
RBC in millions	12	4.758 $\pm$ 0.122	0.422	14	4.466 $\pm$ 0.105	0.394	15	4.392 $\pm$ 0.091	0.352
Hematocrite	12	44.67 $\pm$ 1.17	4.06	14	42.00 $\pm$ 0.77	2.89	15	39.37 $\pm$ 1.09	4.24
S.r. in mm/hr.	12	24.4 $\pm$ 2.2	7.7	14	57.4 $\pm$ 9.0	33.7	15	70.7 $\pm$ 6.6	25.7
Colour index	12	0.989 $\pm$ 0.018	0.061	14	0.951 $\pm$ 0.014	0.053	15	0.931 $\pm$ 0.029	0.110
M.C.H.	12	30.33 $\pm$ 0.55	1.92	14	28.72 $\pm$ 0.57	2.14	15	29.23 $\pm$ 0.87	3.35
M.C.V.	12	94.1 $\pm$ 2.3	7.82	14	93.0 $\pm$ 1.6	6.1	15	90.0 $\pm$ 1.8	7.1
M.C.H.C.	12	32.25 $\pm$ 0.71	2.44	14	31.20 $\pm$ 0.52	1.95	15	31.66 $\pm$ 0.49	1.88
W o m e n									
Hb, in %	7	81.0	—	40	79.1 $\pm$ 1.5	9.3	9	71.9	—
RBC in millions	7	4.251	—	40	4.240 $\pm$ 0.074	0.470	9	3.933	—
Hematocrite	7	39.21	—	40	37.83 $\pm$ 0.60	3.81	9	36.28	—
S.r.	7	38.3	—	40	46.7 $\pm$ 4.8	30.2	9	94.3	—
Colour index	7	0.950	—	40	0.938 $\pm$ 0.017	0.110	9	0.916	—
M.C.H.	7	29.10	—	40	29.01 $\pm$ 0.56	3.53	9	28.21	—
M.C.V.	7	92.1	—	40	90.5 $\pm$ 1.6	9.9	9	92.4	—
M.C.H.C.	7	31.6	—	40	32.04 $\pm$ 0.38	2.42	9	30.32	—

Table 65. *Differences between laboratory figures in the different joint status groups. Polyarthritic men from Uppsala.*

	Difference between		
	D — E	D — F	E — F
Hb. in %	9.1 ± 3.0	12.6 ± 3.1	3.5 ± 3.2
RBC in millions	0.292 ± 0.101	0.366 ± 0.152	0.074 ± 0.139
Hematocrite	2.7 ± 1.4	5.3 ± 1.6	2.6 ± 1.3
S.r.	33.0 ± 9.3	46.3 ± 7.0	13.2 ± 11.2
Colour index	0.038 ± 0.023	0.058 ± 0.034	0.020 ± 0.032
M.C.H.	1.61 ± 0.79	1.10 ± 1.03	0.51 ± 1.04
M.C.V.	1.1 ± 2.8	4.1 ± 2.9	3.0 ± 2.5
M.C.H.C.	1.05 ± 0.88	0.59 ± 0.86	0.46 ± 0.71

Table 66. *Different laboratory figures in the polyarthritic cases from Uppsala, distributed in regard to S.r.*

$M \pm \epsilon(M)$ = mean $\pm$ standard error of the mean; σ = standard deviation.

	S.r. in mm/hr.					
	$\leq 10 \text{ ♂}$			$> 10 \text{ ♂}$		
	$\leq 30 \text{ ♀}$			$> 30 \text{ ♀}$		
	Num- ber	$M \pm \epsilon(M)$	σ	Num- ber	$M \pm \epsilon(M)$	σ
M e n						
Hb. in %	7	95.7	—	34	84.4 ± 1.5	9.0
RBC in millions	7	4.87	—	34	4.36 ± 0.17	0.97
Hematocrite	7	46.00	—	34	40.96 ± 0.68	3.99
Colour index	7	0.984	—	34	0.949 ± 0.015	0.085
M.C.H.	7	30.16	—	34	29.21 ± 0.47	2.73
M.C.V.	7	94.9	—	34	91.7 ± 1.1	6.5
M.C.H.C.	7	31.91	—	34	31.63 ± 0.33	1.93
W o m e n						
Hb. in %	19	85.7 ± 1.9	8.3	37	74.3 ± 1.5	9.1
RBC in millions	19	4.387 ± 0.105	0.457	37	4.092 ± 0.073	0.445
Hematocrite	19	40.87 ± 0.74	3.22	37	36.15 ± 0.58	3.54
Colour index	19	0.982 ± 0.018	0.081	37	0.913 ± 0.019	0.115
M.C.H.	19	30.42 ± 0.69	3.00	37	28.11 ± 0.57	3.50
M.C.V.	19	94.9 ± 2.0	8.7	37	89.0 ± 1.4	8.7
M.C.H.C.	19	32.16 ± 0.35	1.53	37	31.47 ± 0.50	3.05

Table 67. *Differences between laboratory figures in the different S.r.-groups. Polyarthritic women from Uppsala.*

	Difference between cases with S. r. $\leq$ 30 and S. r. $>$ 30 mm
Hb. in %	11.4 ± 2.4
RBC in millions	0.295 ± 0.128
Hematocrite	4.71 ± 0.94
Colour index	0.069 ± 0.026
M.C.H.	2.31 ± 0.89
M.C.V.	5.9 ± 2.5
M.C.H.C.	0.69 ± 0.61

For the women, however, the differences have been calculated and the figures are given in Table 67.

There is a statistically significant difference between the two S.r. groups for Hb and haematocrite, and a statistically probable difference for M.C.H. It is possible that more statistically significant differences could have been shown if the material had been larger. The statistically probable difference for M.C.H. between the two groups seems to be linked up with a microcytosis, perceptible when the material is divided up in this way.

When occasion offers, the present author intends to investigate these matters further on a larger material. The present material has been submitted, however, since it is, to my knowledge, the largest one hitherto presented which has been examined in this way. It has shown that the saturation of haemoglobin in the red blood corpuscles is reduced during a rheumatic infection. It has not been possible to show any reduction of the volume of the red blood corpuscles, probably except in female cases with high S.r.

CHAPTER XIII.

Investigations into serum copper.

In 1942 the present author made determinations of serum copper both in normal persons and in cases of infections of different kinds, describing them in a lecture for the Swedish Association of Internal Medicine in November 1942 (printed 1944). There seemed reason for reviewing these investigations again here, particularly as they were subsequently somewhat enlarged.

It has long (i.e. since about 1840) been known that the body substance of higher organisms contains copper. The last big compilation on the subject of copper and the behaviour of its salts in animal and human organisms was published by Heilmeyer, Keiderling and Stüwe in 1941, and contains 353 references to the literature. Readers are referred to this work for the literature before 1941. However, we should also mention Norinder's book of 1938, though there the copper determinations were carried out with quite other methods. My own bibliography only includes some works on copper published after 1941.

Relatively early on, copper was shown to exist in the liver of subjects with cirrhosis of the liver, and it has been demonstrated in most other organs by different investigators. We. and Wa. Gerlach (1934-1935) made a systematic test of the copper content of the different organs in man (adult and newborn), finding the liver to contain most, having more than twice as much copper per unit of weight than the other organs tested. The liver of the newborn child contained considerably more

than that of the adult — a state of affairs analogous to that in iron.

The investigations described below were performed with the method published in 1941 by Heilmeyer, Keiderling and Stüwe, which is a modification of Callan and Henderson's Na-diaethyldithiocarbamate reaction used earlier on by e.g. McFarlane in 1931 and Tomsett in 1934. The modification consists mainly in reading off the results in a Stufenphotometer in special micro-cuvettes, as in the method used when determining serum iron.

The method will be described, since the present author was forced to introduce modifications in order to reduce the errors of measurement.

Method.

1. The blood was taken in specially washed vessels with platinum iridium needles.

Initial material: 2 cc blood serum, diluted with 6 cc redistilled water.

2. Precipitation of the serum protein with 2 cc trichloroacetic acid, redistilled in glass.

3. Filtering off of the precipitated protein,

4. Pipetting off of 5 cc of the filtrate in a shaking up funnel, followed by the addition 1 cc saturated pyrophosphate solution (in order, as shown by Warburg, to eliminate the iron and manganese present at the same time).

5. Addition of $\frac{1}{2}$ cc concentrated H_3N (which, according to Heilmeyer, enhances the effect mentioned under 4.)

6. Addition of $2\frac{1}{2}$ cc amyl alcohol, intended to absorb the copper carbamate which is formed.

7. Addition of $\frac{1}{2}$ cc 0.1 % Na-diaethyldithiocarbamate solution.

Then follows shaking up, filtering, and reading off of results.

When testing out this method, it was found to be impossible to get reagent and filters which were sufficiently free from copper, which meant that the blind values were very high and differed far too much from one another. Consequently, the

following modifications were introduced, and special measures were taken when cleaning the vessels.

Modifications of the method.

1. The total quantity of reagent required each day was mixed and shaken up with amyl alcohol (this did not, of course, apply to the trichloro-acetic acid, which if necessary must be shaken up isolated). This rendered the reagent practically copper-free.

2. The sample was centrifuged instead of filtered, both to separate out the protein precipitation and to separate the amyl alcohol from the water. The latter procedure is made easier if the tube containing the fluid is chilled. By this means we escape the copper found to be present in the filters, and it also prevents copper being retained in the filters.

In this way the blind values are very low, less than 5 γ % (often 0), and are constant in double tests. Heilmeyer and co-workers submit blind values of about 20 γ %, while previously, ours were not less than 50.

From our experience, three sources of error in the method are worthy of mention:

1. It was found that copper was deposited on the glass vessels when they were dried in a metal drying-cupboard.

2. If the glass vessels are rinsed in warm tap-water, copper is deposited on them; twice distilled water will not remove this, but hydrochloric acid will.

3. Copper was deposited on the walls of the microcuvette, and caused considerable errors when reading off, in the form of raised values. This can be prevented by intensive mechanical cleaning between each test.

Testing of the method on a known amount of copper.

The solution tested was prepared and analysed at the Chemical Institution of the University of Upsala, and contained 163 γ % copper. From this quantity, we found (with a blind value of 0 in 4 tests) an average of 164 γ % for 3 analyses (163, 165, 164).

Testing of the method on a known amount of copper.

Our initial material was a serum whose copper content, taking the mean value of 4 tests (108, 104, 108, 113) was 108 γ %. We enriched the serum with copper to a calculated value of 191.5 γ %. After taking the mean of 4 determinations, our value was 185 γ % (184, 191, 179, 195).

The loss of copper, amounting to about 6 γ %, is probably due to the binding of the copper to the serum protein, since the possibility of its being left behind in the filters has been eliminated by centrifuging the samples.

By adding 1 cc 5 % HCl, 124 γ % of copper could be obtained from the same initial serum; this might reasonably be attributed to part of the copper's being first set free by stronger acid. The enriched serum still showed a smaller quantity of copper, i.e. 202 γ %, instead of the calculated 206 γ %.

Normal material.

The normal material consisted of healthy doctors, medical students, and nurses. The age for the men was 22-36 years (one person of 58 years), and for the women 21-34 years. The material is tabulated below.

Male.				
	Number of cases	$M \pm \varepsilon(M)$	σ	
Hb. in %	15	92.93 ± 1.16	4.50	
RBC in millions	15	4.887 ± 0.051	0.199	
Haematocrite	15	43.83 ± 0.32	1.24	
S.r. mm/hr.	15	3.47 ± 0.32	1.46	
Serum iron	15	100.87 ± 5.1	19.7	
Serum copper	15	110.7 ± 3.1	11.8	
Female.				Difference male-female
Hb.	15	79.80 ± 0.75	2.91	13.3 ± 1.38
RBC	15	4.260 ± 0.051	0.196	0.627 ± 0.072
Haematocrite	15	37.87 ± 0.27	1.06	5.96 ± 0.42
S.r.	15	8.20 ± 0.58	2.24	-4.73 ± 0.69
Serum iron	15	91.00 ± 4.7	18.2	9.87 ± 6.91
Serum copper	15	125.6 ± 3.3	12.8	-14.9 ± 4.5

There were statistically significant differences between men and women in this normal material for Hb, RBC, S.r., and serum copper. As usual, 100 % Hb corresponded in these investigations to 15.3 gm per 100 cc blood. The values for haematocrite, serum iron, and serum copper are the means of double tests.

These normal figures are in good agreement with the normal figures obtained in recent investigations, with the exception that no significant sex difference for the serum iron was obtained in this material; this may be due to its smallness. Heilmeyer and co-workers' mean figures for copper for 15 men were 106.2 ± 2.9 , $\sigma = 16.6$, and for 15 women 106.9 ± 3.1 , $\sigma = 17.07$ — i.e. no sex difference. Cartwright and coworkers' normal figures for serum copper for 25 men were 116 γ % (lowest 92, highest 134), and for 25 women 131 γ % (lowest 103, highest 159). These latter values indicate a sex difference, reverse to that of the serum iron. However, it is impossible to say if the difference between the sexes is significant in their material. In any case, as the table shows, we find a statistically significant sex difference for copper, showing that in this material the women have higher values for serum copper than the men. Further normal figures for copper are to be found in Axtrup (1946). Some of these figures, however, were obtained with other methods.

While the diurnal variations for serum iron have been studied by Vahlquist (1941), Hemmeler (1944), and Waldenström (1946), and the morning values been found to be higher than those in the evening, no such investigations have, to my knowledge, been made as regards serum copper. I have therefore investigated 3 normal subjects and 3 pathological cases and made curves showing variations of serum iron and copper during the 24 hours.

Normal subjects.

Time	Number of observations	Serum iron γ % mean	Serum copper γ % mean
8 a.m.-5 p.m.	12	85.9	112.0
6 p.m.-6 a.m.	15	60.8	114.3

Thus, it is plain that, in these 3 normal subjects, the values for serum iron were lower during the late afternoon and night than in the morning and early afternoon. The serum copper, on the other hand, showed no such variations in these cases. An investigation of 3 pathological cases, 2 of mediumly severe polyarthritis and one of Hodgkins disease with anaemia, also showed there was the same diurnal variation in serum iron, and absence of change in the serum copper, as in the normal cases. It is not known what causes this diurnal variation in the serum iron, or why the serum copper shows no such variation, nor can the present author offer any theory. It should be mentioned that the present author's serum iron samples were all taken in the morning. It is of course conceivable that the variations in the serum iron are due to variations in the function of the iron stores and the iron-consuming organs. It should in any case be pointed out that further investigations are necessary for a definite grasp of the situation.

Pathological material.

This material is outlined in table 68. The values for haematocrite (H-te), serum iron (S.I.) and serum copper (S.C.) are the means of double determinations. The values for white blood corpuscles (W.B.C.), free HCl in the gastric juice and total acidity (T.a.), reticulocytes (Re) and icterus index (I.I.) are also given. All cases had been loaded with $\frac{1}{2}$ gm iron lactate per os, and blood samples for serum iron and serum copper determinations were taken before and respectively 2 and 4 hours after loading. All the patients were men. The addition of (i.m.) to iron loading data means that the patient was given the dose by means of intramuscular injection of iron and ammonium citrate (10 mgm iron).

Table 68. *Pathological material from Upsala.*

Name	Age in years	Diagnosis	Temp.	Hb. %	RBC.	WBC.	Free HCl	S.r. mm/hr.	H-te	Re	I s	C s	I I	Duration
E.H.L.	51	erysipelas faciei	afebrile	93	4.6	7200	—	14	—	—	88	221	—	8 days
											161	196		
											134	195		
E.G.L.	31	polyarthrit. chron.	afebrile	93	5.07	9900	+	6	—	—	53	138	—	12 years
											83	175		
											77	152		
L.S.M.	25	tbc pulm. + pleurit. exud.	subfebrile	87	4.42	7700	+	50	—	8	108	170	3	pleuritis since
											122	162		14 days
P.H.A.	25	sciatica bilat. rheum. infect.?)	afebrile	102	4.52	—	+	20	—	10	88	168	2	7 years
											78	160		
											123	162		
											111	162		
N.O.F.	74	asthma bronch. + sinusitis chron.	afebrile	93	5.22	6200	T.a. 22	—	32	—	27	152	2	> 20 years
											64	144		
											49	128		
S.H.A.	82	bronchit. chron. marasmus	subfebrile	52	2.49	6900	T.a. 6	—	90	18	43	236	3	> 10 years fever since
											53	212		30 days
											55	211		
P.G.H.	54	bronchit. chron. + gangrene pulmon.	febrile	66	4.05	10300	—	42	—	10	155	194	2	4 years periods of fever since
											(i.m.)			about 90 days
											63	197		
B.K.	40	polyarthrit. rheum. chron. + nephrosis (amyloid?)	afebrile	43	2.72	9200	T.a. 9	—	142	22	25	198	—	12 years nephrosis diagnosed 5 months before
											73	52		
											97	75		
											93	66		

W.S.E. ¹	36	pleurit. exud. + stat. post resect. ventr. (1936)	febrile	98	5.14	6200	—	21	40	—	82	195	4	4 days
											39	174		
											33	182		
G.R.E.	18	tbc. pulm. + pleurit. exud.	subfebrile	84	5.5	—	+	41	—	10	63	225	4	pleuritis since 30 days
											(i.m.)			
											160	257		
											151	231		
Do.			»	79	4.54	—	—				51	180		
											(per os)			
											94	187		
L.S.E.	20	tbc. pulm. prim. + pleurit. exud.	subfebrile	87	4.65	6300		64	—	15	23	165	2	tbc. prim. pulm. since 16 months, pleuritis since 10 days
											33	162		
											25	170		
G.S.O.	18	broncho- pneumonia	subfebrile	93	4.40	9100	+	87	38.5	8	19	147	4	3 days
											23	162		
											24	152		
L.E.G.	36	typhoid fever	febrile	84	4.42	8200	—	23	—	—	17	190	5	8 days
											28	183		
											20	198		
E.E.A.	43	empyema pleurae + tbc pulm.	febrile	61	3.13	20900	—	108	—	2	33	233		since 30 days
											(i.m.)			
											95	233		
											51	224		
J.G.E.	58	arterioscle- rosis	afebrile	87	4.07	6500	—	6	—	—	108	131		
											233	117		
											208	114		

¹ in pleura exudate 2 days earlier S.I. = 40 and S.C. = 67 γ %.

In conformity with earlier observations in isolated cases (Krebs, 1928, with Warburg's method; Locke, Main and Rosbach, 1931; Sarata, 1931, Heilmeyer and co-workers, 1941; and others), these cases show raised values for serum copper in infectious states. A statistical calculation has not previously been made, however. For the serum iron in all our 15 infectious cases is $M \pm \epsilon(M) = 64.7 \pm 10.3$, with $\sigma = 39.8$, and for the serum copper $M \pm \epsilon(M) = 173.9 \pm 12.5$, with $\sigma = 48.4$. Both for serum iron and serum copper, the differences from the normal material are statistically significant.

This material, too, shows the antagonism between values for serum iron and serum copper which was pointed out by Sachs, Levine and Fabian in 1935, and by Heilmeyer and co-workers in 1938 and 1941. There is also a deficient rise of the serum iron after iron loading, which circumstance has been described in more detailed in Chapter X. The only exception is case K.A. As well as his chronic uraemia, this patient had also had severe haemorrhoidal and nose bleedings.

There is a low copper value in one case of nephrosis, probably amyloid nephrosis. Sachs, Levine and Fabian demonstrated low copper values in nephritis, and Heilmeyer and co-workers similar values in one case of amyloid.

We know from the investigations of Eisler, Rosdahl and Theorell in 1936 that copper is bound to the serum albumin. The present author thinks it possible that there is a secretion of copper through the kidneys; in which case, this would explain the lowered copper values in the serum.

It is worth mentioning that self dosing experiments with copper loading per os (copper sulphate in solution) were not successful, since as small a dose as 2 cgm caused vomiting.

No case is known where a condition of copper deficiency has been definitely established in men (though it would be interesting to study the state of affairs in renal diseases, particularly the condition with amyloid). Such a condition is known among animals, i.e. sheep and cattle, manifesting itself in a distaste for food and suspended or lowered digestion in the rumen, with a falling-off of condition and low fertility and, in growing animals, poor growth; all these symptoms are rapidly banished

by copper therapy. No anaemia occurs. These disease states arise from a diet poor in copper. In plants, copper deficiency manifests itself as yellow tip, primarily in barley and oats, but also in grain generally (Stenberg, Svanberg and co-workers).

The following facts about the significance of copper in the living organism are also known:

1) It has certainly been proved that copper can cure the milk anaemia produced in white mice. 2) The increased copper content of the blood serum in infections and in states resulting from toxins probably corresponds to some functional significance in the copper in such situations. Of interest in this connection are the investigations showing a warding-off action by means of copper in trypanosomaine infections in mice (Perla, 1934), and the warding-off action against the diphtheria toxin in guineapigs (where, however, ferro-iron in the prophylactic dose had a better effect) (Wohlfeil, 1937). 3) It has been possible to show *in vitro* a bactericidal and growth-inhibiting action in copper in extremely low concentrations (Locke and Main, 1931, and others); copper can also inhibit fermentative processes (Baumgarten and Luger, 1917, and others). On the other hand, it has been shown that copper, as other heavy metals, also has a catalytic effect.

S U M M A R Y.

There is no recent survey of the anaemias arising in infectious conditions. Indeed, very little attention has been paid to these anaemias in the literature; this is understandable, since they usually play a secondary part in the course of the disease. Nevertheless, they are probably one of the very commonest forms of anaemia. The present author has therefore considered it necessary to give a comparatively full review of the literature, as a background to the investigation. Data are also given as to the normal values on record for haemoglobin and red blood corpuscles, and as to indices and absolute figures for the relation between haemoglobin and red blood corpuscles in normal and infectious states. It was hoped that the investigation should give some information of interest not only in regard to infectious anaemia but also in regard to the mechanism of the iron metabolism and the blood formation.

The investigated material consists of 436 individuals, taken from two Swedish hospitals, i.e. from Umeå in Northern Sweden, and from the Academic Hospital in Upsala.

The anaemias concerned are those which set in during the course of a rheumatic infection. This material is compared with normal materials consisting of 256 individuals. Different degree of anaemia are calculated using as limits the normal mean minus once or twice the standard deviation.

When investigating the material we obtained the following results:

1) *The anaemia frequency* in rheumatics in the Umeå material is, under the conditions given, 41.5 and 11.5 % respectively for the men, and 62.8 and 22.7 % respectively for the

women. The cases where anaemia sets in are primarily such as show signs of a special tendency to activity in the disease.

2) *The course of the anaemia* has been followed, showing that the haemoglobin on the whole followed the sedimentation rate, in that the Hb values rise when the S.r. improves, and *vice versa*. The correlation between Hb figure and S.r. is -0.59 ± 0.06 for the men, and -0.31 ± 0.06 for the women. Some cases, particularly among the men, show a resistance to the anaemising influence of the infection. The cases with anaemia show certain differences and have therefore been divided into four groups. The reason for this is given in Chapter XI. This chapter also gives an account of the iron metabolism in normal compared to infectious conditions.

In regard to the symptoms found the following seem to be of interest: *Epithelial symptoms* (rhagades, tongue and nail changes) are appreciably commoner in these cases of rheumatoid arthritis (not only in those with anaemia) than in a normal material and especially common in severer cases and more frequent in women than in men. *Ewald's test meal* was given to 80 men and 136 women with rheumatoid arthritis. It is not possible in this material to reach any definitive conclusions as to the problem of the connection between rheumatoid arthritis, achylia and anaemia, and the author points out on the background of previous investigations that this problem has not yet been finally solved.

3) The main interest of this investigation is centred around the character of the *blood* in different respects.

The colour index is lower in the severer cases of rheumatic infection than in the milder ones: this applies especially to the women.

The diameter of the red blood corpuscles is diminished. 48 cases of rheumatic infection of different degrees of severity have been investigated according to the 'wet' method with an ocular micrometer. There are also indications of increased anisocytosis.

The reticulocytes show an increase in the female pathological material. If their values are followed over some period of time,

they do not seem to follow any law in their behaviour. In this connection the author discusses the term 'blood balance'.

The absolute figures for the relation between haemoglobin and red blood corpuscles have been studied on the Upsala material. In the normal material, the women show an even lower saturation of haemoglobin in the red blood corpuscles than the men, and probably rather larger red blood corpuscles. Compared with the normal material, the saturation of haemoglobin in the red blood corpuscles in the pathological material is lower both for men and for women. The women also show lowered M.C.H. (mean corpuscular haemoglobin). This suggests that the volume of the red blood corpuscle is maintained better in the women than in the men, since M.C.H. is influenced both by the volume of the red blood corpuscles and by the saturation of haemoglobin. The results of this investigation also suggest that, largely speaking, there is no real change of size in the red blood corpuscles of these cases, but rather a change of shape, and that, in rheumatic infections, the bone marrow retains its capacity to produce the stroma of the red blood corpuscles better than its capacity to produce haemoglobin.

4) *The bone marrow* has been studied in 12 female cases of rheumatic infection, and the erythroblasts differentiated according to Naegeli and Rohr. Reasons are found for assuming an increase of the immature erythroblasts in certain cases, suggesting a disturbance in maturity.

5) *The serum bilirubin* is lower in severer cases of rheumatic infection than in milder ones.

The urobilin in passed samples (morning urine) show considerably higher values in the pathological material than in the normal material; this the author is most inclined to interpret as a symptom of liver lesion.

6) *The serum copper* has been investigated with McFarlane and Henderson's methods, with readings made in a micro-cuvette in a Stufen-photometer. The modifications made in the methods are described. The normal material yields a statistically significant difference between men and women. The

mixed infected material which the author investigated shows a statistically significant difference from the normal material, in the form of raised values for the former. In the few cases the author investigated in that respect, the serum copper, unlike the serum iron, shows no diurnal variation. In one case of nephrosis, probably amyloid nephrosis, the author is able to show a lowered figure for serum copper.

7) *The serum iron* is lower in women than in men both in the normal and the pathological material, and is lower in severer and more anaemic cases of rheumatoid arthritis than in slighter ones. The correlation of S.r./serum iron is -0.44 ± 0.09 for men, and -0.26 ± 0.08 for women.

Peroral iron loadings show that the serum iron does not rise as high in cases of rheumatic infection as in normal material, and the increase is less high in severer cases than in milder ones; *iron loadings by intravenous injection* show that the iron leaves the blood stream more rapidly in cases of rheumatic infection than normally.

Peroral iron loading before and after some period of iron therapy shows that the serum iron values taken before the loading are not palpably affected by the therapy, and that those taken after respectively 2 and 4 hours with loading after iron therapy are, if anything, lower than before the treatment. No definite explanation of this can be given.

8) As regards the effect of *iron therapy* it is found that, when the materials are so grouped as to allow for spontaneous recovery from the rheumatic arthritis, it is generally the course of the main disease, and not the iron therapy, that determines the course of anaemia. Curves have been given for two cases who were treated with intravenous iron injections over a considerable period without any apparent effect.

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